REMARKS

Claims 35, 36, 39–43, and 46–49 are pending in this application. Non-elected claims 42 and 43 have been withdrawn from consideration by the Examiner. By this Amendment, claims 35, 36, and 40–43 are amended. No new matter is added.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Enablement Rejection under 35 U.S.C. §112, First Paragraph

The Office Action rejects claims 35, 36, 39, 40, 41, and 46–49 under the enablement requirement of 35 U.S.C. §112, first paragraph. Applicants respectfully traverse the rejection.

The Office Action asserts that the claims include solvates, hydrates, and polymorphs of the recited compounds, and that claim 39 explicitly covers solvates, hydrates, and polymorphs.

None of the claims, including claim 39, recites "solvates," "hydrates," or "polymorphs." Claim 39 recites, "The clathrate compound according to any one of claims 35 and 36, wherein the clathrate compound is a crystalline clathrate compound." Applicants are unclear as to the basis of the Office Action's allegation that claim 39 "explicitly covers" solvates, hydrates, and polymorphs.

"Explicitly covers" is not the same as "does not expressly exclude." Although it may be argued that claim 39 does not expressly exclude solvates, hydrates, and polymorphs, it would certainly be incorrect to argue that claim 39 explicitly covers solvates, hydrates, and polymorphs. Because the claims do not expressly require such limitations, the enablement of such non-recited theoretical embodiments is not required. Claim 39 merely limits claims 35 and 36 to the clathrate compounds that are crystalline. The Office Action fails to establish that the disclosure does not enable one of ordinary sill in the art to make crystalline clathrate compounds within the scope of clathrate compounds defined by claims 35 and 36. The crystalline form is not specifically limited to a solvate, hydrate, or polymorph.

Moreover, claims 35 and 36 are product-by-process claims. As discussed in the March 7, 2012 Amendment, the claimed clathrate compound are obtained by mixing the host compound with the guest compound, and the guest compound is not limited as long as the host compound has the technical features described in claims 35 and 36. Applicants provide herewith References 1 and 2, particularly the following three paragraphs from those references, to further submit that, in general, it was known at the time of the invention that a clathrate compound can be specified as long as the host compound is specified.

Reference 1: J. Mol. Graphics, 1989, 7:12–27, Molecular recognition: designed crystalline inclusion complexes of carboxylic hosts, Edwin Weber.

Reference 2: Topics in Current Chemistry, 1988, 149:45–134, Functional Group Assisted Clathrate Formation – Scissor-Like and Roof-Shaped Host Molecules, Edwin Weber and Mátyás Czugler.

Reference 1, page 12

"Chemists follow two basically different courses with reference to the procedure of cavity formation (Figure 3). One method is to form a *mono*molecular cavity for inclusion of the species to be recognized and bound. The other method is to form a *multi*molecular cavity."

Reference 1, page 13

"By definition, the convergent binding partner of such complexes is specified as the *host*, while the divergent (and included) species is called the *guest*. Host and guest form an integral whole that is termed *supermolecule* or *supramolecular aggregate*."

Reference 2, page 50

"The examples might have illustrated that functional groups (e.g. OH, COOH, NH_2), as they are a component of classical crystal inclusion compounds, are usually used for construction, cross-linking, and stabilization of the host lattice molecules, e.g. via coordination or H-bonding (Fig.6b). To speak with a newly developed classification system on inclusion compounds (see

Chapter 1 of Vol. 140), those are 'true' clathrates and not 'coordinatoclathrates' (cf. Fig.6, for a more detailed specification see Fig. 15 in Chapter 1 of Vol. 140)."

For at least the reasons discussed above, Applicants respectfully submit that the claims sufficiently meet the enablement requirement under 35 U.S.C. §112, first paragraph. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

II. Rejection under 35 U.S.C. §112, Second Paragraph

The Office Action rejects claims 35, 36, 39, 40, 41, and 46–49 as being indefinite under 35 U.S.C. §112, second paragraph. By this Amendment, the terms "reacting" and "reacted" are amended to respectively read "mixing" and "mixed." Reconsideration and withdrawal of the rejection are respectfully requested.

III. Rejections Under 35 U.S.C. §102

A. Gladych

The Office Action rejects claim 35 under 35 U.S.C. §102(b) over Gladych et al. Applicants respectfully traverse the rejection.

The claimed clathrate compound does not include the adduct of 1,3-benzenedicarboxylic acid, 4-hydroxy-, compound with 2-aminoethanol (1:1) disclosed in Gladych.

Reconsideration and withdrawal of the rejection are respectfully requested.

B. Aoki

The Office Action rejects claim 36 under 35 U.S.C. §102(b) over WO 99/11609 to Aoki et al. Applicants respectfully traverse the rejection.

WO 99/11609 is the international publication of the instant application. Withdrawal of the rejection is respectfully requested.

IV. Rejoinder

Applicants respectfully request rejoinder of the withdrawn method claims upon allowance of the elected claims.

V. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

James A. Oliff
Registration No. 27,075

Jeffrey R. Bousquet
Registration No. 57,771

JAO:JRB

Attachments:

Reference 1: J. Mol. Graphics, 1989, 7:12–27, Molecular recognition: designed crystalline inclusion complexes of carboxylic hosts, Edwin Weber.

Reference 2: Topics in Current Chemistry, 1988, 149:45–134, Functional Group Assisted Clathrate Formation – Scissor-Like and Roof-Shaped Host Molecules, Edwin Weber and Mátyás Czugler.

Date: September 17, 2012

OLIFF & BERRIDGE, PLC
P.O. Box 320850
Alexandria, Virginia 22320-4850
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry of this filing; Charge any fee due to our Deposit Account No. 15-0461

Molecular recognition: designed crystalline inclusion complexes of carboxylic hosts

Edwin Weber

Institute for Organic Chemistry and Biochemistry, University of Bonn, Bonn, FRG

Recently there has been a gradual drift of organic chemists into research relevant to biology. This has resulted in a rich array of sophisticated model systems. Ultimately, such models are intended to imitate the specific recognition of substrates. The lattice-type inclusions are expected to be particularly useful in this respect. This paper explains the basic ideas of a new strategy for directed lattice inclusion called "coordination-assisted clathrate formation." Besides matching sizes and shapes, this strategy makes extensive use of functional group interactions between a host and a guest molecule, allowing molecular recognition in the solid state. In particular, the carboxylic group is demonstrated as a sensitive site of host molecules for interaction (multicontact binding) with guest molecules of different H-bond donor and/or acceptor strength involving alcohols, carboxamides, dimethyl sulfoxide and carboxylic acids. Hosts refer to molecules of different geometric shapes (scissor-type, roof-shaped and small-ring acids). We will look at structural aspects of the H-bonded supramolecular aggregates formed between host and guest that are responsible for the mutual recognition properties.

Keywords: molecular recognition; crystalline inclusion complexes; carboxylic hosts, X-ray crystal structures; H-bonding

Molecular recognition is fundamental for biotic processes.[1] It is also important in bioorganic and abiotic chemistry.[2] The field is growing rapidly.[3] Many topics are involved — catalysis, compound transport and separation, regulation, enzyme mimicry, host-guest systems, new materials, and so on. Thus, there is great potential in applications.[4,5]

GENERAL APPROACH

Each molecule has a specific surface that is characterized by size, shape and functional sites.[6] These properties should apply to molecular recognition. Consequently, recognition of one molecule by another may involve matching attributes as specified above.[7] In other words, we want to characterize a full complementary relationship between the two chemical species — the molecule to be recognized, and the molecule that effects recognition. Hence, we need a cavity of designed dimensions for probing the shape and size of the molecule under consideration and complementary functional groups for chemical identification (Figure 1a).

It is useful to combine both principles in a sense of what is suggestive of an enzymic active site,[1] or a functionalized cavity for endo-binding (Figure 1b). Some of the fundamental considerations[4] leading to this conclusion are illustrated in Figure 2.

Exo-binding (Figure 2a), by way of functional group interaction that does not profit from a cavity-core relationship, naturally is of inferior value in size and shape recognition compared to *endo*-binding (Figure 2b), which has this relationship. Also, as Figure 2 shows, it is difficult to use the full functional group capacity of both partners in the case of exo-binding, since all functional groups are *divergent*. Consequently, the molecule under consideration is not realized as an integral whole, but only segmentary, giving rise to mistakes in recognition. In the case of endo-binding, the functional groups are *convergent/divergent*. Hence, they can face each other with the complete set of functional groups. This shows, in principle, that endo-binding is superior to exo-binding in molecular recognition. Translation into practice of the unfolded conception, then, is a problem of forming a designed cavity.

PRINCIPLES OF CAVITY FORMATION AND DEFINITIONS

Chemists follow two basically different courses with reference to the procedure of cavity formation (Figure 3). One method is to form a *mono*molecular cavity for inclusion of the species to be recognized and bound. The other method is to form a *multi*molecular cavity. Examples are macrocyclic rings[3b] (such as crown compounds[8] or cyclophanes[9]) and crystal cavity inclu-

Address reprint requests to Prof. Dr. E. Weber at the Institute for Organic Chemistry and Biochemistry, University of Bonn, Gerhard-Domagk-Str. 1, D–5300 Bonn–1, FRG.
Received 12 September 1988

This paper was presented at the Symposium on Molecular Recognition: Its Role in Chemistry and Biochemistry, held in Sopron, Hungary, 24–27 August, 1988.

Table 1. Inclusion compounds of host molecule 1

Guest compound	Host:guest mol ratio*
Methanol	1:2
Ethanol	1:2
1-Propanol (n-propanol)	2:1
2-Propanol (isopropanol)	1:2
1-Butanol (n-butanol)	1:1
2-Butanol (sec-butanol)	1:1
2-Methyl-1-propanol (isobutanol)	1:1
2-Methyl-2-propanol (t-butanol)	1:1
1-Pentanol (n-pentanol)	1:2
2-Methyl-1-butanol	2:1
2-Methyl-2-butanol	1:2
4-Methyl-1-pentanol	1:1
Benzyl alcohol	1:1
Trichloroethanol	1:1
Ethylene glycol	1:1
Propylene glycol	1:1
Acetic acid	2:3 (1:1)
Propionic acid	2:1
Lactic acid	1:1
Formamide	1:2
N-Methylformamide	1:2
N,N-Dimethylformamide (DMF)	1:2
Acetylacetone (2,4-pentanedione)	1:1
Acetonitrile	1:1
Nitromethane	1:1
Dimethyl sulfoxide (DMSO)	1:1
Bromobenzene	1:1

*Determined by NMR integration after a drying period of 12 h at 0.5 Torr for each compound

Table 2. Preference of guest binding by 1 (two-component solvent system)

Recrystallization solvent compd mixt (equimol ratio)	Relative guest excess, %GE*	Sizes of H-bonded rings
MeOH/2-BuOH	>95	[12]/[10]
EtOH/t-BuOH	92	[12]/[10]
EtOH/*$HOCH_2CH_2OH$*	> 95	[12]/[24]
MeOH/*EtOH*	46	[12]/[12]
EtOH/2-PrOH	79	[12]/[12]
1-PrOH/*2-PrOH*	29	[12]/[12]

*Species in italics preferentially enclathrated

Table 3. Inclusion compounds of host molecule 2 with alcohols

Guest alcohol	Host:guest mol ratio*
1-PrOH	1:1
1-BuOH	1:1
t-BuOH	1:1
1-PentOH	1:1
1-OctOH	2:1
$HOCH_2CH_2OH$	1:2

*Determined by NMR integration after a drying period of 12 h at 0.5 Torr for each compound

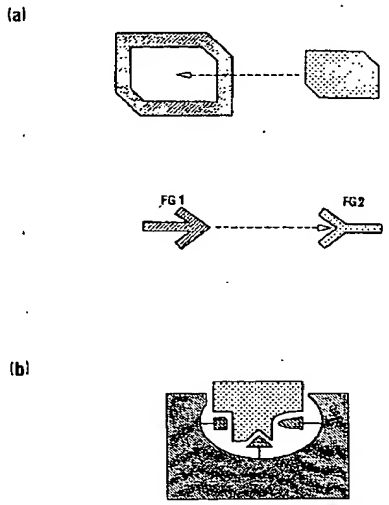


Figure 1. Principles of molecular recognition: (a) the role of steric fit and complementary functional groups (FG); (b) active site analogy

sion.[3b,3c] in another view termed *cavitate* and *clathrate* inclusions.[10]

By definition,[4a,7] the convergent binding partner of such complexes is specified as the *host*, while the divergent (and included) species is called the *guest*. Host and guest form an integral whole that is termed *supermolecule* or *supramolecular aggregate*.[4b]

DEVELOPING A NEW INCLUSION STRATEGY: COORDINATION-ASSISTED CLATHRATE FORMATION

Both methods of cavity formation specified in Figure 3 have pros and cons. The disadvantage of the cavitate approach is due to the troublesome synthesis of macrocyclic hosts, but the host cavities are well defined. Compared with this, clathrates can be formed by considerably simpler host molecules, since here the cavity is generated by aggregation of several small host molecules in the crystal lattice. On the other hand, the hosts were subject to a high degree of randomness, and only recently have some helpful design principles for clathrate hosts been developed.[11-16] Possibly the most general one in application came from our group and is called *coordination-assisted clathrate formation*.[14,17]

As suggested by the term,[10] a coordinatively assisted clathrate, or *coordinatoclathrate*, involves a hybrid between a complex and a clathrate (Figure 4a). Thus, coordinatoclathrates combine attributes of coordinative complexes and of lattice-dependent clathrates, and this is the reason that they make possible a high degree of selectivity in different directions, including chemoselectivity and constitutional selectivity, according to the origin (see Figure 4a).[14,17]

Consequently, a corresponding coordinatoclathrate host (Figure 4b) consists of two components: (1) a *bulky basic skeleton* that makes available lattice cavities typical of a clathrate and (2) *appended functional groups (sensor*

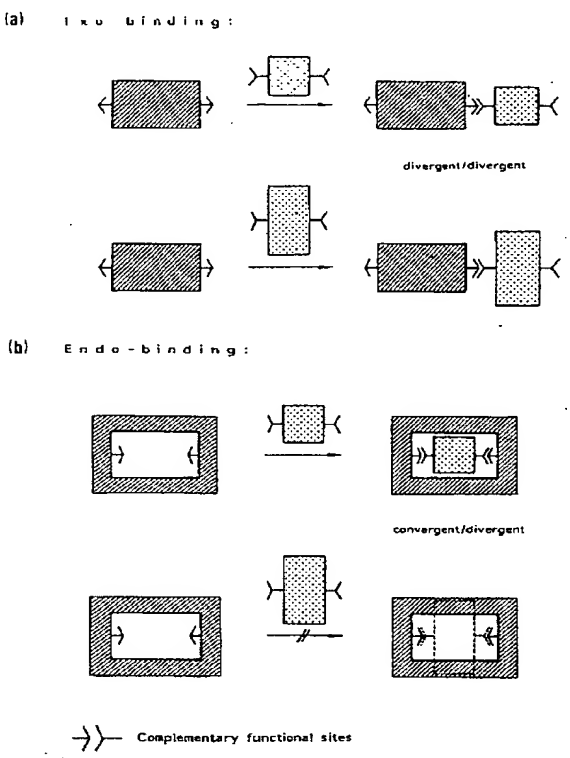


Figure 2. Exo- and endo-binding

groups) that manage the coordination to the included guest substrate.

By using a host molecule endowed with these properties, the basic idea is to create a situation in a crystal (Figure 5) in which highly affine functional groups of a host molecule are prevented from contacting for steric reasons. Yet these functions are available to complementary groups of sterically lower demanding (smaller) guest molecules that are able to bridge the gap. Normally, without steric repulsion, the pure hosts would form a dimer.

A typical host molecule based on these ideas, then, must meet these criteria:

(1) It should be *bulky* in constitution, to provide low-dense packing in the crystal.
(2) It should have a *rigid* conformation, to maintain the cavity structure and not to collapse.
(3) It should have appropriately placed and highly *affine* functional groups for reasons mentioned above.
(4) It should be aimed at a *balanced* overall shape of the molecule that will help stabilize the crystal packing in general.

A typical molecule that approaches this ideal is simple 1,1'-binaphthyl-2,2'-dicarboxylic acid (**1**) (abbreviated hereafter as BNDA; see Figure 6). The molecule has a scissor-like shape with two large lipophilic (the aromatic units) and two smaller hydrophilic terminals; (the carboxylic groups). So it is amphiphilic and possesses a well-defined geometry that favors clear orientation in the crystal.

RECOGNITION OF ALCOHOLS

Using the Scissor-type Carboxylic host BNDA

Recrystallization of compound **1** (BNDA) from different alcohols (see Table 1)[14] results in the formation of well-developed channels of approximately 6–7 Å diameter (Figure 7a) with a stoichiometric number of solvent molecules inside the channel.[17] The channels mainly have an apolar surface that is interrupted periodically by hydrophilic narrowings consisting of the carboxylic groups (Figure 7b). The cross-section of electron densities in this channel area (Figure 7c) clearly shows two facing carboxylic groups held in a noninteractive distance that follows closely the basic idea of Figure 5, namely, formation of a specific gap in the crystal lattice. Here are the sites at which the accommodated guest molecules contact the host.

This is more evident in Figure 8, which shows a detail of the crystal structure of inclusion compound **1**·MeOH (1:2).[14] Bridging the gap is via two molecules of methanol providing a set of complementary H-bonds to the carboxylic groups. Thus, a 12-membered ring system of coupled H-bonds is formed [mean (acid)O(−H)···O(MeOH) = 2.610 Å, 172°; mean (MeOH)O(−H)···O(acid) = 2.761 Å, 156°].

Besides methanol, other alcohols (Figure 9b) are also involved in the same binding pattern of H-bridges with the BNDA host, as demonstrated by crystal structures[14] (e.g., ethanol and isopropanol, but also n-propanol, which results in the uncommon 2:1 host:guest stoichiometry; the former have 1:2 stoichiometry).[18] This means that the stoichiometric factor is not a reliable source of information on the mode of host:guest binding in this field of compounds.

Other alcohols, such as sec-butanol or tert-butanol (inclusion stoichiometry 1:1 in both cases) bind in a 10-membered ring fashion of H-bridges to the host (Figure 9a)[14,18] (e.g., the symmetric scheme of H-bonds changes to an asymmetric one that involves two carboxylic groups, but only one alcohol [mean (acid)O(−H)···O(alcohol) = 2.556 Å, 171°; mean (alcohol)O(−H)···O(acid) = 2.685 Å, 171°; mean (acid)O(−H)···O(acid) = 2.625 Å, 161°]). Evidently, this is a result of the more voluminous alkyl residues of these alcohols, demonstrating the influence of second rank (say steric) interactions between host and guest. In these circumstances, it is not possible to accommodate two neighboring molecules of alcohol in the host channel. Crystal structures[14,18] point to the same conclusion.

The case of the inclusion compound with bivalent ethylene glycol also merits mention. Here, a huge centrosymmetric 24-membered ring of coupled H-bonds including four carboxyl and four hydroxyl groups is formed [mean (acid)O(−H)···O(alcohol) = 2.634 Å, 169°; mean (alcohol)O(−H)···O(acid) = 2.828 Å, 167°]

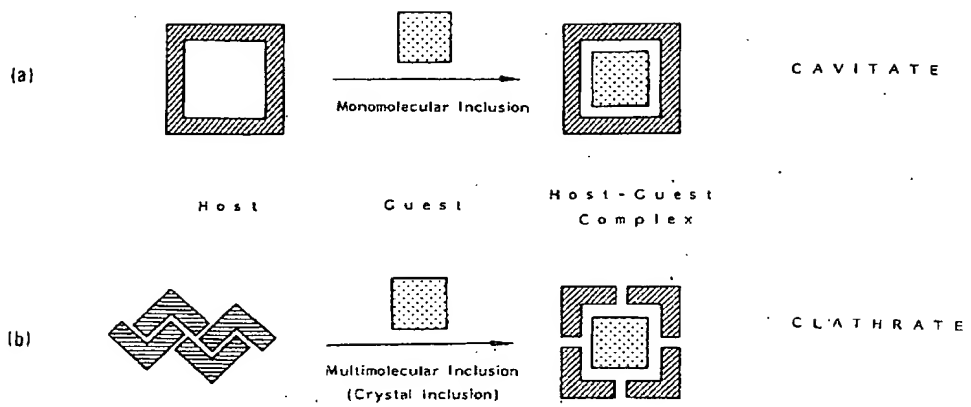


Figure 3. Strategies of inclusion formation

(Figure 9c).[14] Because of the extended pattern, the original channel structure cannot be detected any longer.

Albeit of some variance, the inclusion compounds of BNDA with alcohols show a common structural behavior, namely, the formation of *closed H-bonded loops* at the contact surface of host and guest, which may reflect a characteristic recognition pattern between carboxylic and hydroxylic groups, or carboxylic acids and alcohols.

Examination of some of the inclusion selectivities from two component mixtures of alcohols — which means preferred inclusion of one alcohol species when a second one is present — suggests in the first place that the highest discrimination occurs when differing ring sizes of the formed systems of H-bridges between host and guest are involved (Table 2).[14]

In the second place, the alcohol leading to the larger system of H-bonds is normally preferred (e.g., ethanol [a 12-membered ring] is preferred over tert-butanol [a 10-membered ring], or ethylene glycol [a 24-membered ring] is preferred over ethanol). Otherwise, the discrimination is lower. Thus, the particular contact pattern may also be connected with the stability properties of the different inclusion compounds in a systematic way.

Using the roof-shaped carboxylic host FADA

To probe the generality of this behavior, we studied the recognition properties of other carboxylic hosts with regard to alcohols. Such an example of different constitution is compound **2** (9,10-ethano-9,10-dihydroanthracene-trans-11,12-dicarboxylic acid; see Figure 10), the simple Diels-Alder adduct of fumaric acid to anthracene (abbreviated as FADA).[17,19,20]

This host molecule was developed by a geometric approach similar to **1**. While the preceding BNDA-host **1** is suggestive of a pair of scissors (Figure 6), **2** relates to a roof (Figure 10). Compared to **1**, FADA (**2**) has a more rigid structure. Hence, adaptability to differently sized alcohols is supposed to be reduced or influenced in a way, but the net tendency of alcohol binding with **2** should exist.

In fact, FADA (**2**) is not capable of forming crystal inclusions with the small alcohols methanol and ethanol, but only with the higher homologues from 1-propanol up to 1-octanol (Table 3).[19,21] A crystal inclusion of **2** with ethylene glycol is also obtained. The favorite host:guest stoichiometry here is 1:1; BNDA inclusions showed almost to the same extent 1:2 and 1:1 stoichiometries (Table 1).

Nevertheless, looking at Figure 11, which shows a detail of the X-ray crystal structure of **2**·1-BuOH,[19,20] one realizes that host and guest are linked together in a 12-membered ring of H-bonds [(acid)O(−H)···O(BuOH) = 2.599 Å, 176°; (BuOH)O(−H)···O(acid) = 2.741 Å; H atom not located] corresponding to the inclusions of BNDA with small alcohols (Figure 9b). Here (Figure 11), it is more voluminous 1-butanol that is involved in the H-bonded ring system, but the dimensions of the rings[17] are largely the same, as seen in Figure 8.

The reason for the 1:1 host : guest stoichiometry for the FADA-inclusion instead of the 1:2 stoichiometry for the BNDA inclusion is a direct host-host interaction via functional group dimerization [O(−H)···O = 2.646 Å, 173°] (Figure 11), which formally reduces the original bivalency of the host molecule to monovalency. Properly speaking, we deal with a bivalent supramolecule as host, whose components are two individual molecules of **2**. This dimer supramolecular host unit is observed in all inclusion structures involving **2**[17,21] (see below); it even exists in the crystal structure of solvent-free **2**.[19,20]

The most important point, however, is the exact correspondence of the recognition pattern between alcohols and carboxylic hosts, respective of their constitution. One may learn from this behavior that at best steric conditions by the lattice, the 12-membered ring of H-bridges formed between the given functional groups possibly represents a standard mode of interaction in the crystalline state. This statement is supported by other examples in the literature[22,23] not related to the scissor- and roof-type hosts.

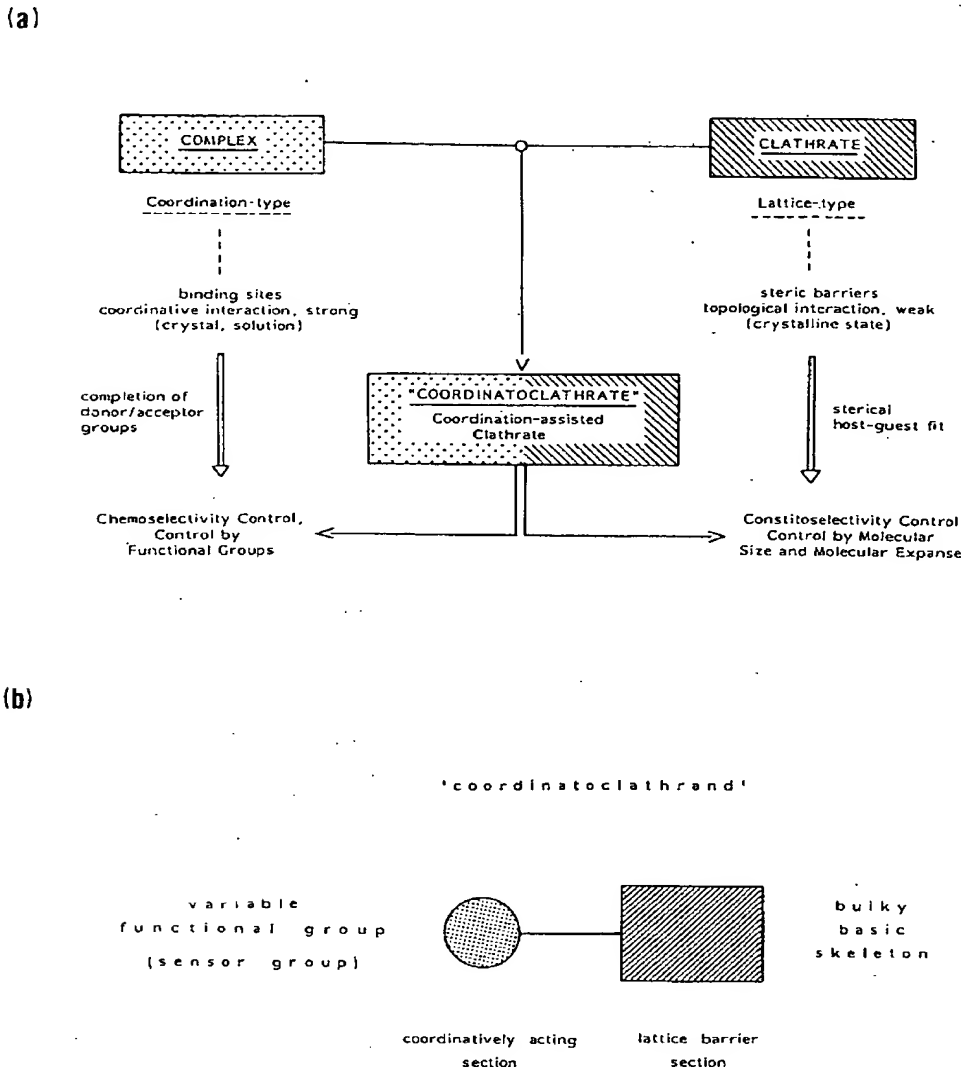


Figure 4. Coordinatoclathrate concept (a) and abstracted structure of a coordinatoclathrate host (b): definitions, relations, and functions of control

However, based on recent X-ray studies, a third new family of carboxylic hosts determined by a small-ring as a primary building element shows different behavior.[24]

Using small-ring carboxylic hosts

Introducing a rigid small-ring unit as a structural building block into host compounds requires a strategy as follows: On principle, both the scissor- and the roof-type hosts **1** and **2** refer to configurational rigid structures (Figure 12a) characteristic of a central axis with lipophilic (aromatic units) and hydrophilic groups (carboxylic functions) on each terminal. For reasons of geometry, the terminals may be occupied by four groups at the most, and their distribution is more or less fixed (one lipophilic and one hydrophilic group on each side), which presents limitations.

A formal extension results if the axis determining the structural element is replaced by a triangle or a quadrangle (Figure 12b); now more than four groups (up to eight) can be accommodated in a high variety and with new geometries. Adaptation to specific requirements of guest molecules is thus easier.

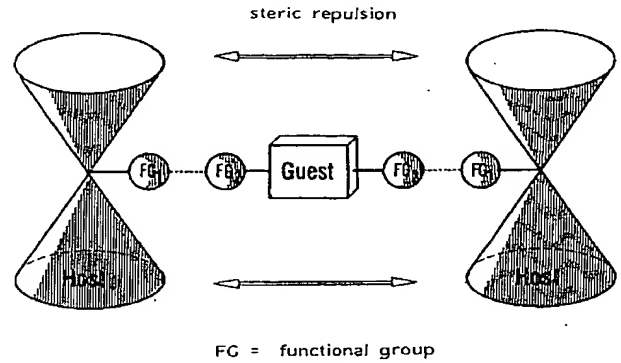


Figure 5. Coordinatoclathrate formation (diagramatic representation)

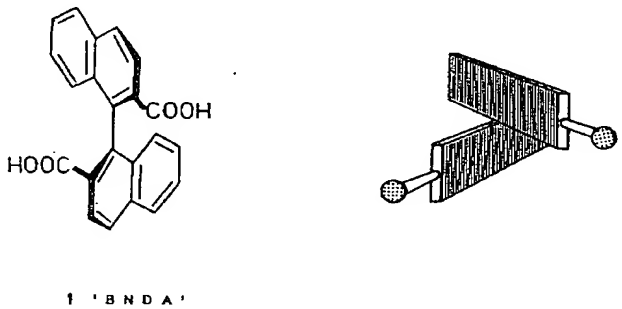


Figure 6. Prototypical host molecule **1** *and graphic abstraction*

Because of the limited number of inclusion structures presently available,[18] we will discuss only one representative of each host family (three- and four-membered ring constitutions), namely host compounds **3** and **4** (Figure 13).

As expected, both hosts form crystalline inclusions with alcohols, but with different species and in a very different scale.[24] The cyclobutano host **4** allows only clathrate formation with methanol, while the cyclopropano host **3** does not. The latter, however, renders possible inclusions with ethanol, 1-propanol, 2-propanol, 2-butanol, and tert-butanol. Thus, **3** is typical of clathrate formation with relatively bulky alcohols and discriminates methanol, while **4** is just the opposite.

The stoichiometries are different in both cases. Inclusion compounds with **3** show 1:1 host:guest stoichiometries, while **4**·MeOH has 1:2 stoichiometry. This suggests that **3**, in virtue of the *cis*-geometry of the carboxylic groups that favor an intramolecular H-bond, externally behaves as a monovalent host; *trans*-dicarboxylic acid **4**, however, is bivalent. Obviously, sizes and shapes of crystal cavities are also determined by the different host geometries.

Referring to the alcohol inclusions of **2** (see above), stoichiometries are not suitable for assessing binding modes between host and guest. This was realized again with the X-ray crystal structures of inclusion compounds **3**·tert-BuOH (1:1), **3**·EtOH (1:1), and **4**·MeOH (1:2).

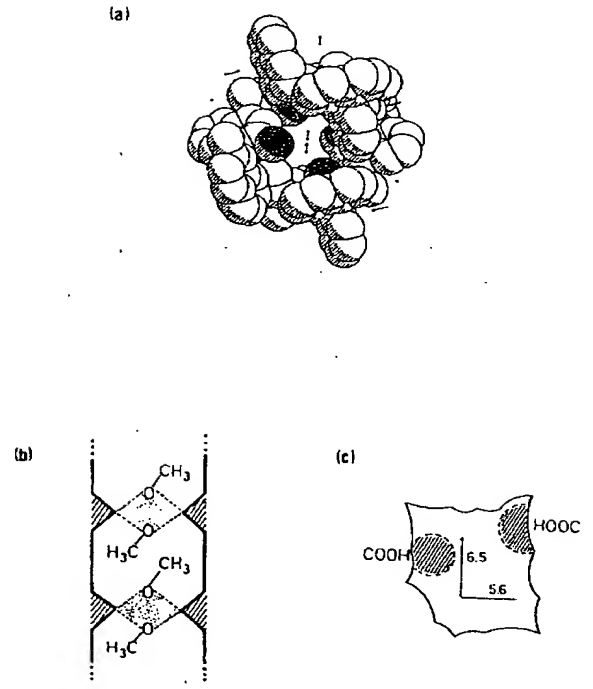


Figure 7. Inclusion channel in **1**·*MeOH (1:2). (a) Space-filling illustration (view down the channel axis, methanol molecules represented as small sticks); (b) schematic representation of the longitudinal section (hatched triangles and dotted squares represent polar areas, while the rest is of apolar property); (c) approximation of the van der Waals cross-section (dimensions are in Å; hatched regions represent O atoms of the host matrix, continuous solid lines indicate surfaces of apolar attribute)*

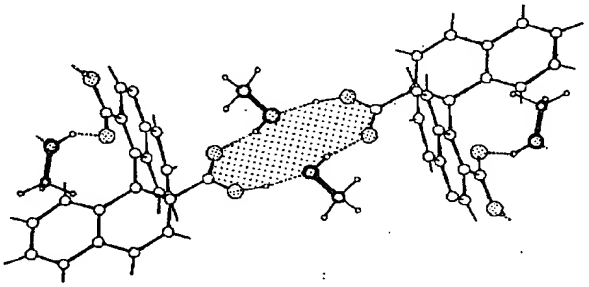


Figure 8. Packing excerpt from the crystal structure of **1**·*MeOH (1:2) showing the 12-membered supramolecular loop of H-bonds (shaded region). In all Figures H-bonds are specified as broken lines, O atoms are dotted, and N atoms are hatched*

Figure 14 shows the structure of **3**·tert-BuOH (1:1).[24] At a glance, one would think of the presence of cyclic H-bonds between host and guest (Figure 14a), but this is not true. Instead, the carboxylic groups of the achiral host and the tert-butanol molecules form a *helix* of H-

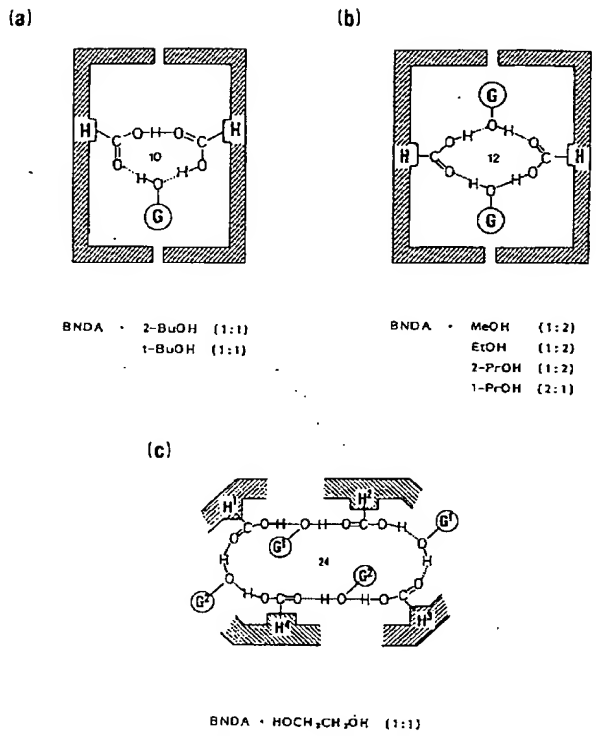


Figure 9. Diagrammatic representation of supramolecular bonding modes (H-bridge systems) found in the alcohol inclusions of **1** *(bold H and G denote host and guest, respectively)*

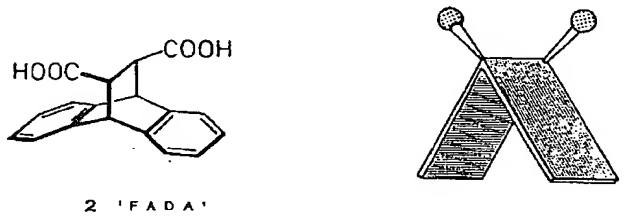


Figure 10. Perspective formula of host molecule **2** *and graphic abstraction*

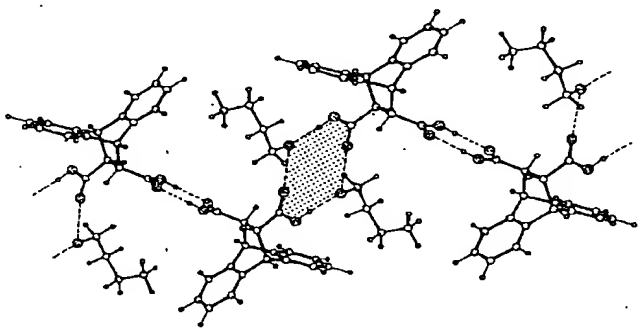


Figure 11. Packing excerpt from the crystal structure of **2**·*1-BuOH (1:1) showing the 12-membered supramolecular loop of H-bonds (shaded region); nonshaded loops of H-bonds refer to direct host-host interaction*

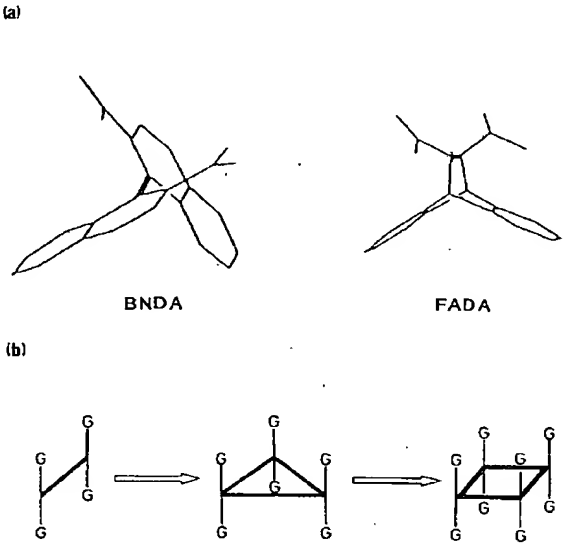
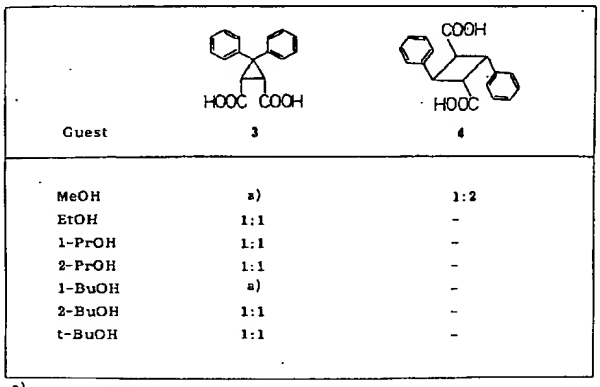


Figure 12. Dimensional approach of building elements (bold type) in host design. (a) Skeletal drawings of scissor-type and roof-shaped hosts **1** *and* **2** *showing the central molecular axis. (b) Extension to a triangular or quadrangular building block (G stands for a substituted group)*

bonds (Figure 14b) that has a topological relation only to the expected loop. In detail, one intramolecular H-bond [O(−H)···O = 2.552 Å, 170°] involving the *cis*-carboxyls and two intermolecular H-bridges [O(−H)···O = 2.566 Å, 155° and 2.861 Å, 144°] between host and guest contribute to form the helix.[25] Similar conditions exist at the **3**·EOH (1:1) inclusion.[18] Another remarkable point is that **3**·tert-BuOH (1:1) crystallizes in an enantiomorphous space group ($P2_12_12_1$); thus, individual crystals are optically active.

The free host compound **3**, which is given for comparison, also has an enantiomorphous space group ($P2_1$) that involves not a helical but a *linear* system of H-bonds [O(−H)···O(intra) = 2.513 Å, 162°; O(−H)···O(inter) = 2.590 Å, 180°] (Figure 15).[18] This means that only when **3** is in contact with a guest molecule is the helix formed. The inclination to spiral H-bonds in host-guest complexes possibly is connected with the particular geometry of **3**.

A behavior similar to the inclusions of **3** (i.e., no closed loops of H-bonds) is shown by **4**·MeOH (1:2).[24] Because of the trans-configuration of the carboxylic groups, instead of *cis* for **3**, *zigzag lines* of H-bonds between host and guest are formed [(acid)(O−H)···O(MeOH) = 2.594 Å, 164°; (MeOH)O(−H)···O(acid) = 2.743 Å, 167°] (Figure 16b). The structure can be described as



Guest	3	4
MeOH	a)	1:2
EtOH	1:1	-
1-PrOH	1:1	-
2-PrOH	1:1	-
1-BuOH	a)	-
2-BuOH	1:1	-
t-BuOH	1:1	-

a) Low tendency to crystallize.

Figure 13. Constitutions of small-ring hosts **3** *and* **4**, *and specification of their inclusion compounds with alcohols*

a framework of channels including the molecules of methanol H-bonded to the host (see Figure 16a). In a manner of speaking, the channel walls have seams made of the carboxylic groups where the guest molecules bind. The channel dimension can accommodate only small alcohols, such as methanol.

Hence, we deal with topologically different H-bonding between alcoholic guests inside a channel or channel-like matrix of carboxylic hosts as schematized in Figure 17: (a) along an infinite *zigzag*-line; (b) in a *helical* fashion; and (c) in the way of *closed loops*. Examples are **4**·MeOH (1:2) (Figure 16), the alcohol inclusions of **3** (as seen in Figure 14) and the alcohol inclusions of **1** and **2** (see Figures 8 or 9 and 11), respectively.

Despite the differences in binding topology and thus of the recognition pattern with reference to alcohols and carboxylic acids, there is still one common point in the large number of discussed inclusion structures: *cooperativity*,[26] indicated by the coupled systems of H-bonds existing between host and guest. One may connect it with the strong or relatively strong H-donor/H-acceptorship of the contributing functional groups. To learn more, we shall turn to inclusions of the given hosts (and derivatives) involving other guest functional groups and discuss a few of their structures.

RECOGNITION OF CARBOXAMIDES (DIMETHYLFORMAMIDE)

Dimethylformamide (DMF, Figure 18a) is an organic molecule of suitable size for lattice cavity inclusion.[3b,3e] It provides a polar group that is rather a proton acceptor than a donor, as obvious from its resonance formulae (Figure 18a). Would it allow cooperative binding to the carboxylic hosts and, if so, which is the particular recognition pattern with reference to this guest molecule?

Supposing similarity to the alcohol inclusions, this would require C-H···O type interactions,[27] and one may expect 11- and 14-membered rings, as specified in Figures 18c and 18d, respectively. However (based on the present results), only half of it is true, namely the formation of the large 14-membered H-bonded ring that includes two formyl and two carboxyl groups, while the smaller 11-membered ring species with one formyl and two carboxyls is not observed. Instead, a "monomeric" 7-membered H-bonded ring, as specified in Figure 18b, is found several times, unlike the alcohol case, where this ring type does not occur. Examples of each of the two ring constitutions are given by the DMF inclusions of **2** (FADA) and of **1**-analogous **5** (spiro-type host).

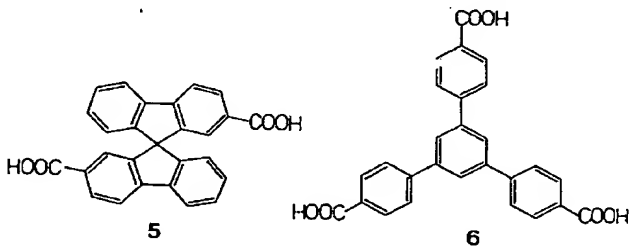


Figure 19a shows a packing excerpt of the **2**·DMF (1:1) inclusion compound studied by X-ray crystal structure.[19] The 14-membered (dimeric) ring of H-bridges including host and guest is seen in the center [O(−H)···O = 2.623 Å, 179°; C(−H)···O = 3.240 Å, 160°]. There is also a direct carboxylic group dimer per host molecule [O(−H)···O = 2.616 Å, 170°], which is typical of **2** (c.f., 1-BuOH inclusion compound of **2**; see Figure 11). Another remarkable detail of the structure is the use of *anti*-oriented hydrogens at the carboxylic groups for guest recognition. Normally, the carboxylic hydrogens are involved in *syn*-fashion, as obvious from Figure 19b, which illustrates the 7-membered (monomeric) ring formation in the crystal structure of **5**·DMF (1:2).[17,28] Here, both carboxylic groups of the host are involved in guest recognition via a direct two-point contact to the formyl part of DMF [O(−H)···O = 2.593 Å, 167°; C(−H)···O = 3.112 Å, 126°].

However, this is not always the case, since the two H-bridge contacts are classified as different in binding strength; the formyl-H bond is the weaker of the two. Hence, one can assume that under environmental constraints, the formyl-H bond is broken first. In doing so, the two-point interaction reduces to a simple one-point interaction that has a lower qualification in molecular recognition, as seen in Figure 2. This exact behavior is shown by the **1**·DMF (1:2) inclusion compound (Figure 19c).[17,29] One of the two DMF molecules of the asymmetric unit is bound in the 7-membered ring fashion to the bicarboxylic host [O(−H)···O = 2.692 Å, 152°; C(−H)···O = 3.054 Å, 129°]; the other is in *linear single* contact only [O(−H)···O = 2.613 Å, 159°; formyl-H *anti* to the host carbonyl], owing to packing conflicts.

An inclusion structure showing DMF exclusively in the linear state of H-bond interaction with carboxylic groups [O(−H)···O = 2.611 Å, 178°] is in **6**·DMF (1:3) (Figure 19d).[30] Here, probably due to crystal forces, the DMF molecule is turned around the O–H···O bond so as to incline its molecular plane through 36.2° to the plane of the carboxyl group it coordinates.

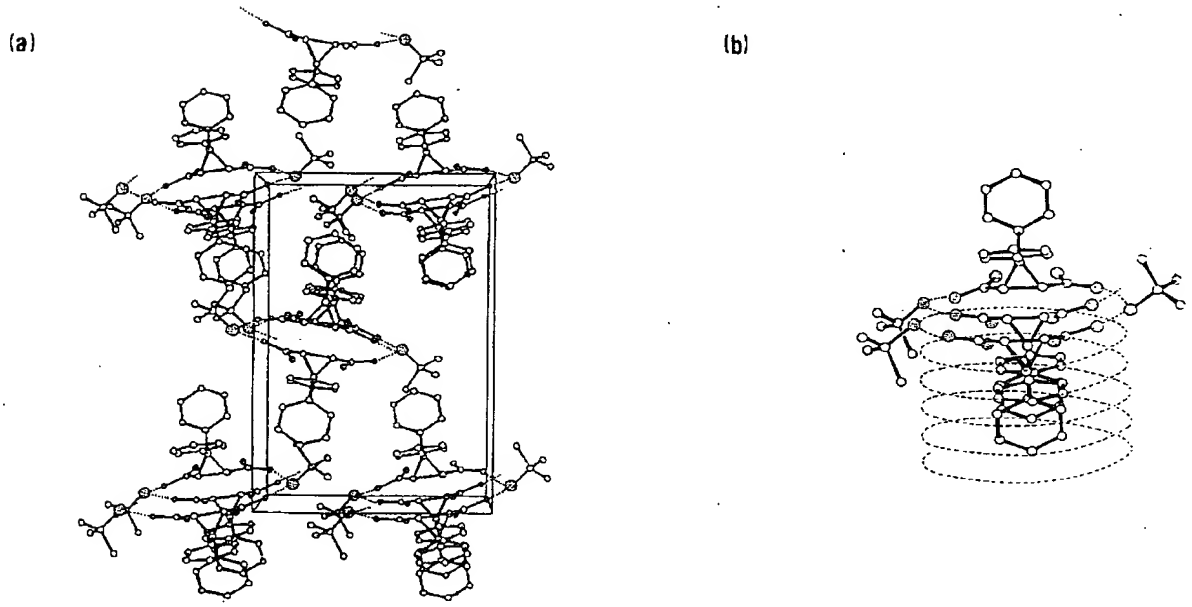


Figure 14. (a) Packing excerpt; (b) detail from the crystal structure of **3**·*t-BuOH (1:1) showing the supramolecular helix of H-bonds*

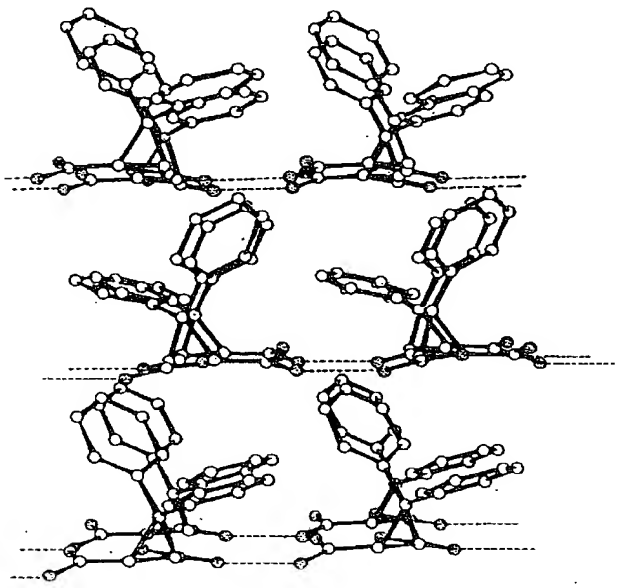


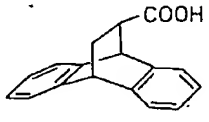
Figure 15. Packing excerpt from the crystal structure of free host compound **3** *showing the linear chains of H-bonds*

In the absence of a formyl-H, such as in homologous acetamide as a guest molecule, a two-point interaction with a host carboxyl group naturally is not possible. Hence, the host-guest binding is expected to be weak. The expectation is confirmed by the inclusion structure of **4**·acetamide (1:2) (Figure 20).[18] The loose bonding between host and guest [O(−H)···O = 2.600 Å, 154°] becomes apparent in the disorder of the acetamide molecule that is in two orientations in the crystal. The plain guest molecule is nearly perpendicular to the carboxyl plane it coordinates. Host and guest molecules form separate stacks in the crystal.

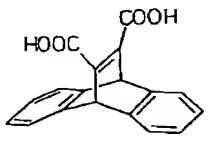
RECOGNITION OF DIMETHYL SULFOXIDE

Besides DMF, dimethyl sulfoxide (DMSO, Figure 21a) is another organic molecule that can interact with carboxylic hosts via two specific sites of different binding strength. According to the resonance formulae given in Figure 21a, it should be a relatively strong H-acceptor and weaker H-donor to a carboxylic group.

Considering the interaction of DMF with carboxylic groups (see Figures 19a and 19b), H-bonding systems most expected for the DMSO inclusions of carboxylic hosts are the 8- and the 16-membered ring constitutions specified in Figures 21b and 21c. Remarkably, the 18-membered (dimer) ring is not found here (with reference to five crystal structures,[17,29,31] but only the small 8-membered ring, inclusive of related sypramolecular structures due to packing interference. The major points of host-guest interaction and molecular recognition in this field are illustrated by Figures 22a–22c, involving hosts **1**, **2**, and **8**.



7



8

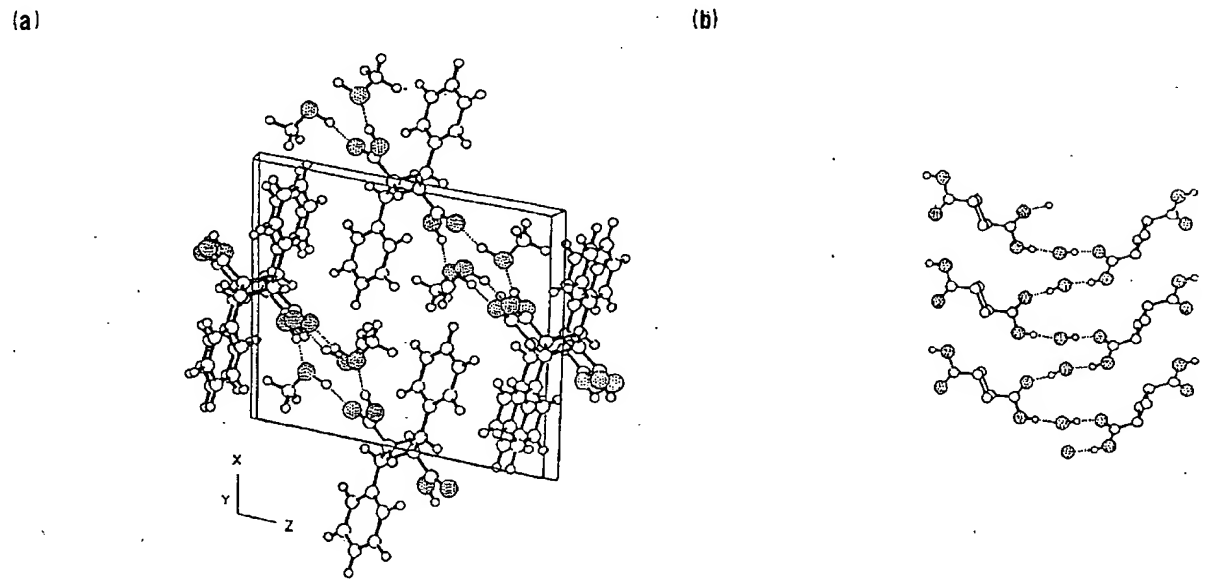


Figure 16. Packing excerpt (a) and detail (b) from the crystal structure of **4**·*MeOH (1:2) showing the supramolecular zigzag chains of H-bonds*

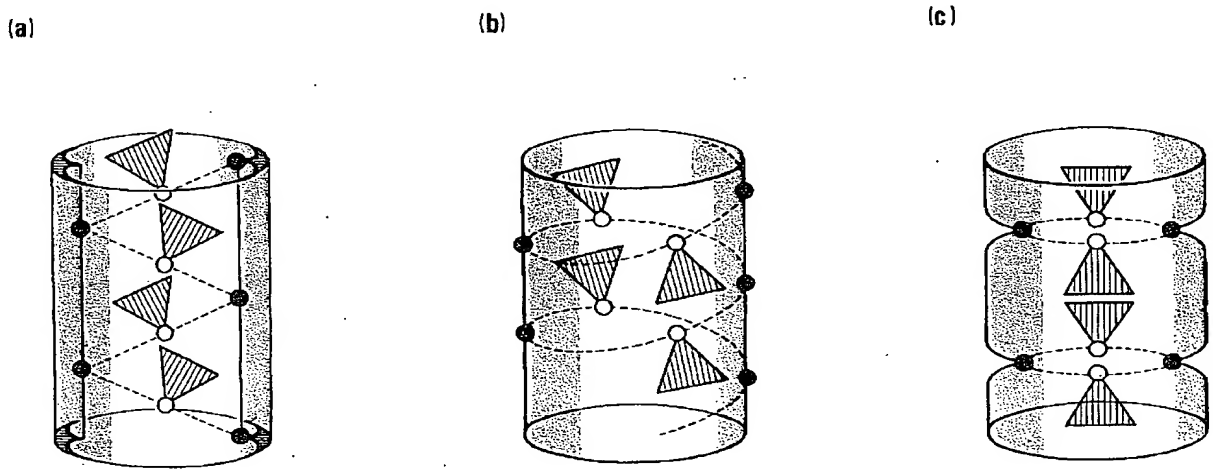


Figure 17. Diagrammatic representation of the supramolecular binding (H-bond) topology of alcohol molecules (hatched triangles) inside the carboxylic host channels (broken lines represent H-bonds; filled circles are contact sites of the host, open circles of the guest). (a) Zigzag-line; (b) helical; and (c) closed-loop mode of interaction

Figure 22a shows the asymmetric unit of the **2**·DMSO (1:1) inclusion complex.[17,21] The distances indicate a strong H-bond between hydroxy and S=O [O(−H)···O = 2.606 Å, 167°] and suggest a very weak C−H····O type interaction[27] between the carbonyl-O and a methyl-H of DMSO [C(−H)···O = 3.346 Å, 148°], thus giving rise to an 8-membered cyclic recognition pattern for the DMSO molecule. A direct host-host interaction via carboxylic group dimerization, typical of this host molecule (as seen in Figures 11 and 19a) and responsible for the 1:1 stoichiometry, is also found here.

The same cyclic recognition pattern for DMSO, including a weak C–H····O interaction between host and guest [C(−H)···O = 3.32 Å, 134°], is in the 1:1 DMSO inclusion of a corresponding mono acid **7**.[17,31]

That the C–H····O contact under discussion has to

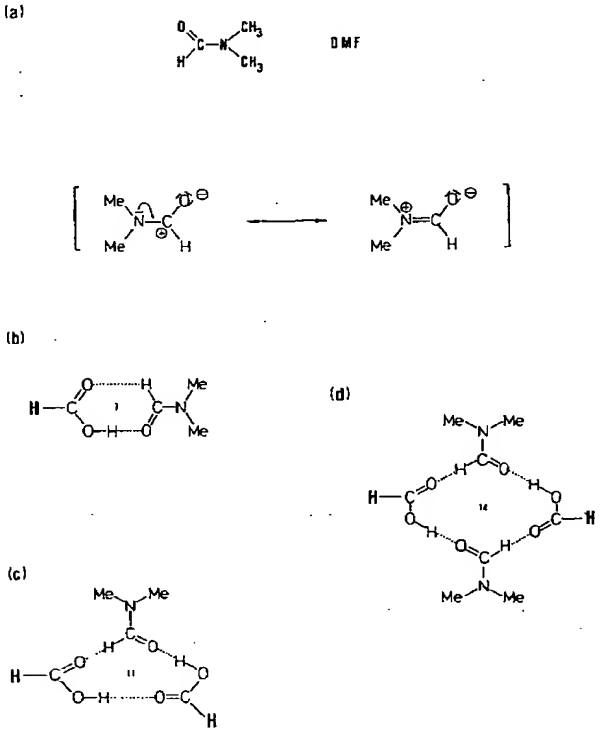


Figure 18. (a) Constitutional and resonance formulae of dimethylformamide (DMF); (b)–(d) possible modes of cyclic H-bond interactions between DMF and a carboxylic host (the bold H stands for host, H-bonds are represented by broken lines; the numbers denote ring sizes)

be classified as very weak is evident from Figure 22b, which shows the supramolecular unit of the 1:2 (host: guest) DMSO inclusion of **8** (unsaturated analogue of FADA, 2).[17,31] One molecule of DMSO (S2) of the bivalent complex is in the *cyclic* state of H-bonding [O(−H)···O = 2.562 Å, 161°; C(−H)···O = 3.38 Å, 140°], as described before. The other molecule of DMSO (S1), however, lacks the weak secondary contact to the host carboxyl it coordinates [O(−H)···O = 2.563 Å, 172°]. The methyl groups of this DMSO species are turned away from the respective carboxyl group; hence, a linear mode of binding follows. Yet, the crystal packing reveals an analogous C–H···O contact of the linearly bound DMSO molecule to the carboxyl group of a neighboring host molecule [C(−H)···O = 3.29Å, 144°]. Thus, coordination of DMSO is to the same sites for both guest molecules, on principle, but the binding topology is different, due to steric conflicts.

In the case of the 1:1 DMSO-inclusion of BNDA (**1**) (Figure 22c)[17,29] we find another interesting variant of interaction between DMSO and carboxylic hosts (see Figure 22b). As before, a cyclic and a linear recognition pattern also coexist here, this time involving the DMSO sulfoxide oxygen as a double acceptor site of H-bonds [O(−H)···O = 2.652 Å, 146°; O(−H)···O = 2.635 Å,155°; C(−H)···O = 3.308 Å, 161°]. This results in the formation of infinite H-bonded chains composed of alternating host and guest molecules running through the crystal. Consequently, molecular recognition of DMSO is effected by two host molecules via three contacts.

Possibly, there is no suitable packing for the BNDA molecule in the crystal to act as a bivalent host for two DMSO molecules, as intended. To some extent, an analogous behavior is also indicated in the corresponding DMF inclusion (Figure 19c), where one of the two DMF molecules of the supramolecular complex is in a two-point contact to BNDA, while the other binds only linearly.

RECOGNITION OF CARBOXYLIC ACIDS

Upon consideration, the ideal complement for a carboxylic function could be the carboxylic group itself. Indeed, it is a trivial property of carboxylic acids to form H-bonded dimers[32] (Figure 23.) This way of acting is frequently seen in monomolecular (non-host–guest) crystals[33] ($R^1 = R^2$ in Figure 23) and may be interpreted as a mode of self-recognition. Would it also work in host-guest fashion ($R^1 \neq R^2$ in Figure 23? The answer is not clear at the moment.

In most of the all-carboxylic acid inclusions we have studied [**1**·acetic acid (2:3), **2**·formic acid (1:2), **2**·acetic acid (1:1), and **2**·propionic acid (1:1)],[21,34] host and guest form separate dimers (R^1 goes together with R^1 and R^2 with R^2, c.f. Figure 23), or the host recognizes the host and the guest recognizes the guest, with no specific contact between the two species.

This is illustrated in Figure 24a, which shows a packing excerpt of the **2**· propionic acid (1:1) inclusion compound.[20,34] The host molecules linked together via carboxylic group dimerization [O(−H)···O = 2.661 Å, 163°; O(−H)···O = 2.651 Å, 165°] form infinite zigzag chains. These chains are arranged so that tunnels are created parallel to the *c*-axis of the crystal. The propionic acid molecules form H-bonded dimers [O(−H)···O = 2.647 Å, 167°], which reside in these tunnels (i.e., the guest dimers behave as a certain hydrophobic species with no specific interaction to the host). They are retained only by steric barriers of the host matrix. Accordingly, they are organized as in classical clathrates[11] whose recognition properties depend mainly on steric fit.

While the acetic acid and propionic acid inclusions of **2**[21,34] are isomorphous, the inclusion of **2** with small formic acid (Figure 24b) has a different structure,[20,34] suggested already by the different stoichiometries (1:1 in the case of propionic and acetic acid, but 1:2 for formic acid). The great difference between the two structures (see Figures 24a and 24b) is that in **2**·formic acid (1:2), in addition to host-host and guest-guest, host-guest carboxylic group dimers are also found, which is the direction of molecular recognition we intend.

The building principle of this inclusion structure (Figure 24b)[34] is as follows. There are supramolecular host-

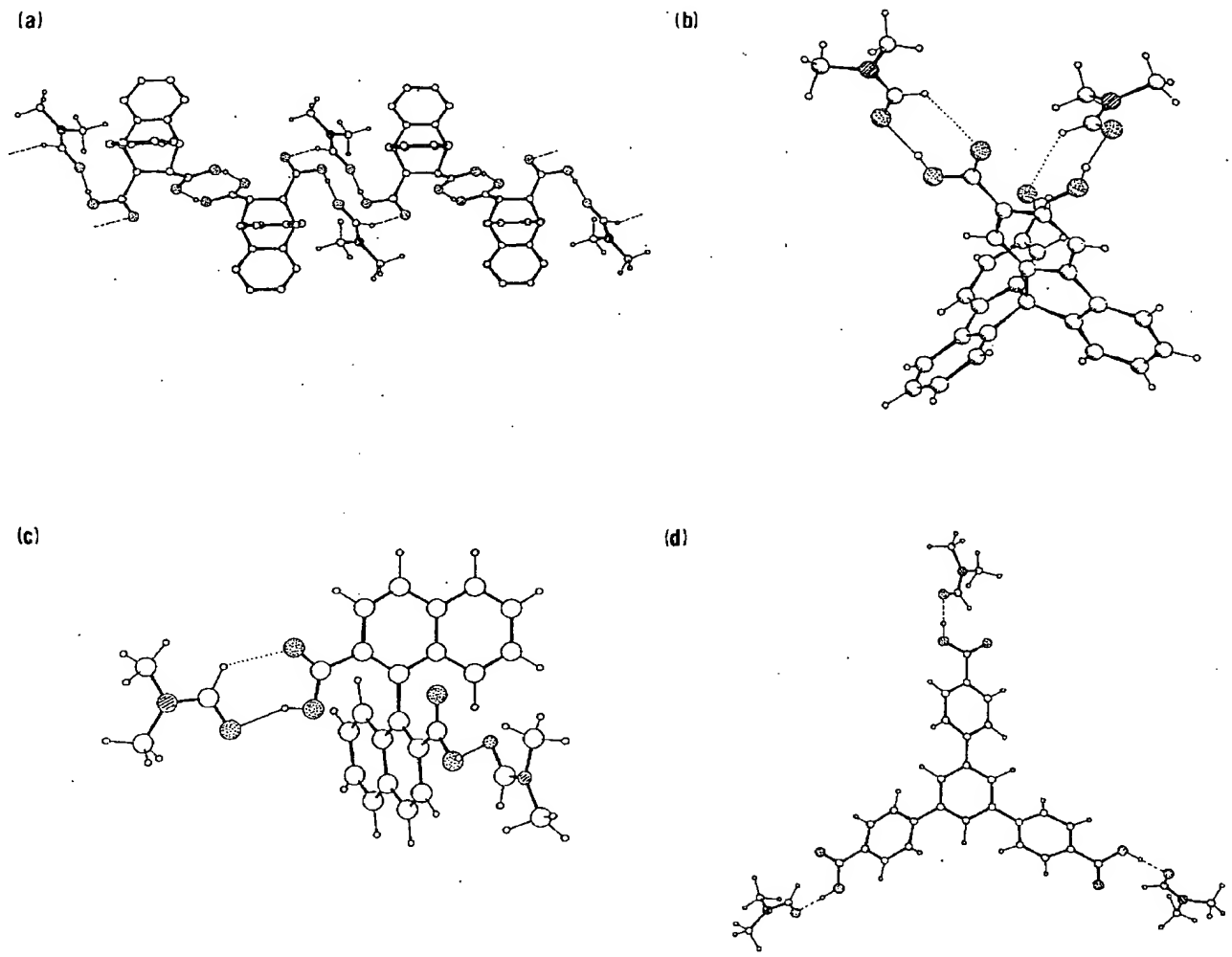


Figure 19. Recognition characteristics of dimethylformamide emanating from crystal structures of inclusion compounds between carboxylic hosts and DMF. (a) 2·DMF (1:1); (b) 5·DMF (1:2); (c) 1·DMF (1:2); (d) 6·DMF (1:3); (a) packing excerpt; (b)–(d) molecular structures. Strong and weak H-bonds are represented by thin and broken lines, respectively

guest associations with 2:2 stoichiometry [O(−H)···O = 2.647 Å, 175°; O(−H)···O(F) = 2.690 Å, 174°; (F)O(−H)···O = 2.676 Å, 172°]. These aggregates are linked together by van der Waals type forces to form the crystal lattice that provides cavities where H-bonded dimers of the guest acid residue [O(−H)···O = 2.640 Å, 146°]. These dimers have no specific interaction to the host molecules. Thus, molecular recognition by means of functional group interaction with the host is not fully exhausted here, but only in part.

Roughly, the host matrix in the propionic acid and acetic acid inclusions of **2** may be related to the structure of free host **2**,[17,19] while the formic acid inclusion of **2**, in a certain way, bears features of the corresponding DMSO inclusion (see Figure 22a). The modes of interaction in **1**·acetic acid (2:3)[17,34] are similar to **2**·formic acid (1:2) (i.e., host-host, host-guest, and guest-guest carboxylic group dimers all exist in the crystal).

We are not aware of any example where host-guest dimers of carboxylic groups are exclusively formed. The finding raises the question of whether the pK_a -values of host and guest acid play a role for the formation of a particular aggregate structure and whether this behavior is confined to carboxylic acids only or applies also to molecules with other functional groups of high H-bond capability, such as amides. Studies along these lines[35] are promising, since designed aggregate structures of H-bonded acids and amides in the crystalline state[36] are suspected as useful tools for different problems in organic solid state chemistry[37] and materials science.[38]

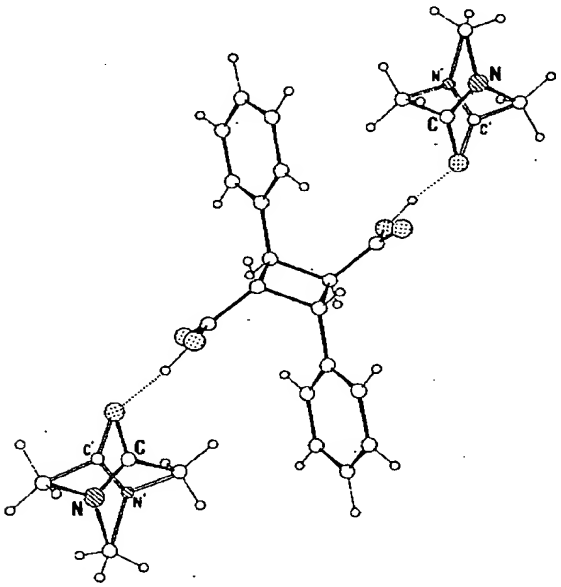


Figure 20. Molecular structure of **4**·*acetamide (1:2); the guest molecules show twofold disorder for the C and N atoms*

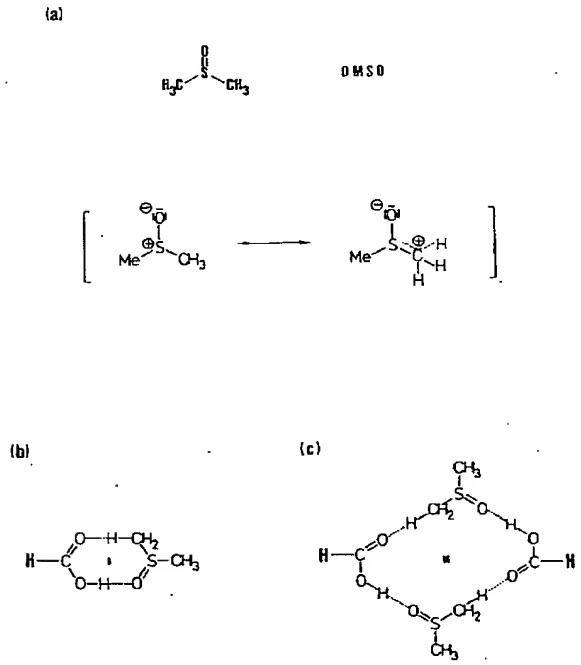


Figure 21. (a) Constitutional and resonance formulae of dimethyl sulfoxide (DMSO); (b) and (c) possible modes of cyclic H-bond interactions between DMSO and a carboxylic host (the bold H stands for host; H-bonds are represented by broken lines; the numbers denote ring sizes)

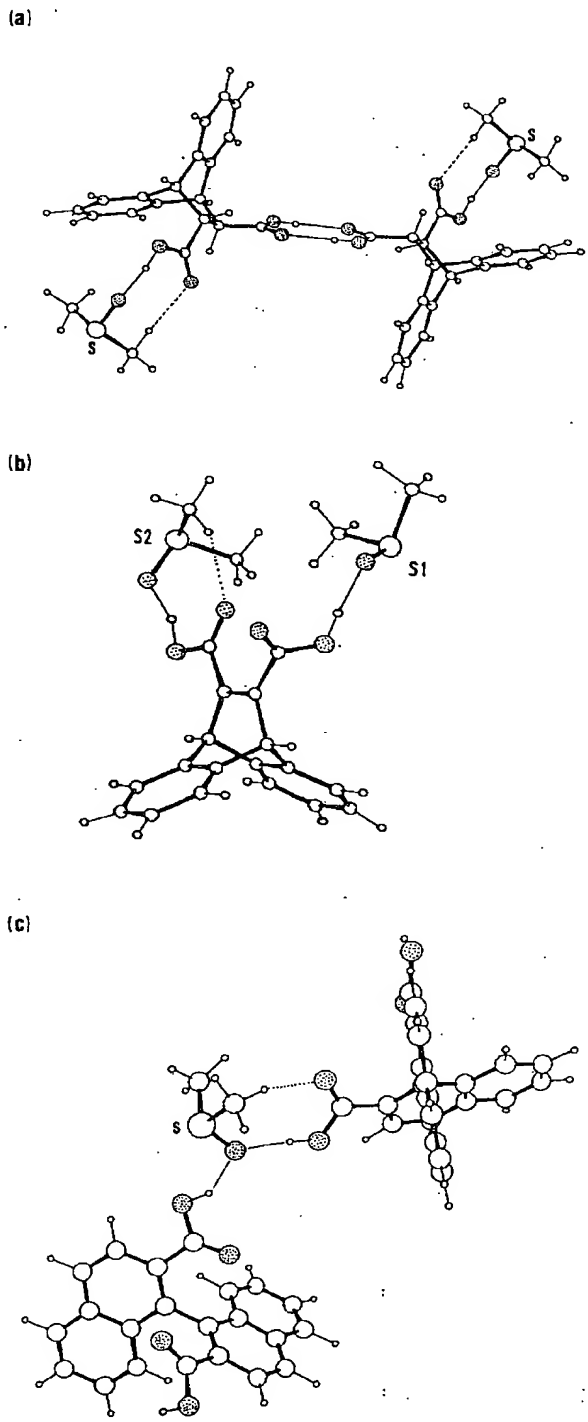


Figure 22. Recognition characteristics of dimethyl sulfoxide (DMSO) emanating from crystal structures of inclusion compounds between carboxylic hosts and DMSO (molecular structures; strong and weak H-bonds are represented by thin and broken lines, respectively). (a) **2**·*DMSO (1:1); (b)* **8**·*DMSO (1:2); (c)* **1**·*DMSO (1:1).*

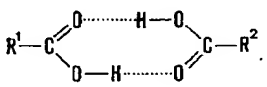
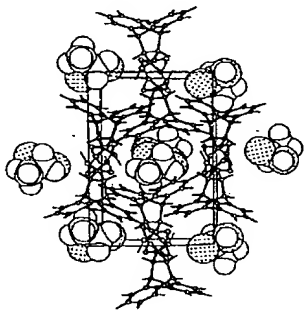


Figure 23. Conventional carboxylic dimer

(a)



(b)

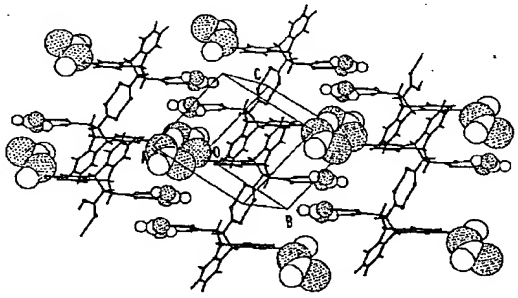


Figure 24. Packing relations of (a) 2·propionic acid (1:1) and (b) 2·formic acid (1:2); complementary stick-style and space-filling representations of host and guest molecules, respectively. In (b), the small spheres refer to the host-bound guests; O atoms dotted

CONCLUDING REMARKS

Carboxylic groups appropriately placed at a rigid molecular backbone are capable of molecular recognition in a crystalline host matrix using a specific H-donor/H-acceptor relationship to complementary functionalized guests, as schematized in Figure 25. Details have been discussed for guests with hydroxy, methylsulfinyl, and formyl counterpart groups that are suggested as H donors of decreasing order.[39] In principle, acids by themselves are also suitable guest partners for a carboxylic host, as shown in the previous section.

Nevertheless, a great variety of other guest molecules with potential H-donor/H-acceptor behavior, such as nitromethane, acetonitrile, malonodinitrile, acetylenes and ketones, remain to be studied in a similar way. We have formed ideas of how their recognition by carboxylic hosts might take place, and we look forward keenly to seeing whether our expectations are met or not.

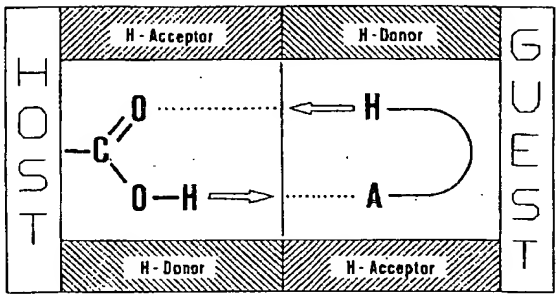


Figure 25. Fundamental H-donor/H-acceptor relationship in molecular recognition, demonstrated by carboxylic hosts

Considering the generality of the "coordinative assistance principle" in clathrate formation[17] that makes feasible a defined and predictable recognition in heteromolecular crystalline assemblies, the carboxylic acids discussed here are only a small sector in a sea of potential host molecules. I am sure that such hosts that have amide or hydroxy functions[40] are found just as effective in molecular recognition as carboxylic acids, but on different territories. Preliminary results[35,41] point to this fact.

ACKNOWLEDGEMENTS

I gratefully acknowledge the crystallographic work of Dr. I. Csöregh (University of Stockholm, Sweden) and Dr. M. Czugler (Central Research Institute of Chemistry, Hungarian Academy of Sciences, Budapest, Hungary) that underlies this paper. I am also indebted to Prof. P.Kierkegaard (Stockholm) and Prof. A. Kálmán (Budapest) for their continuous interest in this research, and I thank Dr. M. Hecker and Dipl.–Chem. W. Seichter for drawing the Figures. The work at Bonn was supported financially by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

REFERENCES

1 (a) *Chemical Recognition in Biology*, Chapeville, F. and Haenni, A.L. (Eds.). Springer-Verlag, Berlin, Heidelberg, 1980. (b) Stryer, L. *Biochemie*, 2d ed., Vieweg, Wiesbaden, 1983. (c) *Enzyme Mechanisms*, Page, M.I. and Williams, A. (Eds.). Royal Society of Chemistry, London, 1987

2 (a) *Applications of Biochemical Systems in Organic Chemistry, Part II (Techniques of Chemistry, Vol. X)*, Jones, J.B., Sih, C.J., and Perlman, D. (Eds.). Wiley-Interscience, New York, 1976. (b) Dugas, H. and Penney, C. *Bioorganic Chemistry*, Springer, New York, 1981. (c) *Chemical Approaches to Understanding Enzyme Catalysis*, Green, B.S., Ashani, Y. and Chipman, D. (Eds.). Elsevier, Amsterdam, New York, 1982. (d) *Host Guest Complex Chemistry – Macrocycles*, Vögtle, F. and Weber, E. (Eds.). Springer-Verlag, Berlin, Heidelberg, 1985. (e) *Design and Synthesis of Organic Molecules Based on Molecu-*

lar Recognition, Van Binst, G. (Ed.). Springer-Verlag, New York, 1986
3 (a) *Progress in Macrocyclic Chemistry, Vols. 1–3*, Izatt, R.M., and Christensen, J.J. (Eds.). Wiley-Interscience, New York, 1979, 1981, 1987. (b) *Inclusion Compounds, Vols. I–III*, Atwood, J.L., Davies, J.E.D. and MacNicol, D.D. (Eds.). Academic Press, New York, 1984. (c) *Host Guest Complex Chemistry I–III (Topics in Current Chemistry, Vols. 98, 101, 121)*, Vögtle, F. and Weber, E. (Eds.). Springer-Verlag, Berlin, Heidelberg, 1981, 1982, 1984. (d) *Biomimetic and Bioorganic Chemistry, I–III (Topics in Current Chemistry, Vols. 128, 132, 136)* Vögtle, F. and Weber E. (Eds.). Springer-Verlag, Berlin, Heidelberg, 1985, 1986, 1986. (e) *Molecular Inclusion and Molecular Recognition – Clathrates I and II (Topics in Current Chemistry, Vols. 140 and 149)*, Weber, E. (Ed.). Springer-Verlag, Berlin, Heidelberg, 1987 and 1988.
4 (a) Cram, D.J. Von molekularen Wirten und Gästen sowie ihren Komplexen (Nobel-Vortrag). *Angew. Chem.* 1988, **100**, 1041–1052; *Angew. Chem., Int. Ed. Engl.* 1988, **27**, 1009. (b) Lehn, J.–M. Supramolekulare Chemie – Moleküle, Übermoleküle und molekulare Funktionseinheiten (Nobel-Vortrag). *Angew. Chem.* 1988, **100**, 91–116; *Angew. Chem., Int. Ed. Engl.* 1988, **27**, 90
5 (a) Weber, E. Crown ethers. *Ullmann's Encyclopedia of Industrial Chemistry, Vol. A8*. VCH Verlagsgesellschaft, Weinheim, 1987, 91–97. (b) Weber, E. Crown compounds – Properties and Practice. *Phase Transfer Catalysts – Properties and Applications*. Merck-Schuchardt, Darmstadt, 1987, 33–76
6 Meyer, A.Y. The size of molecules. *Chem. Soc. Rev.* 1986, **15**, 449–474
7 Cram, D.J. Präorganisation — von Solventien zu Sphäranden. *Angew. Chem.* 1986, **98**, 1041–1060; *Angew. Chem., Int. Ed. Engl.* 1986, **25**, 1039
8 Weber, E. Crystalline uncharged molecule inclusion compounds of unintended and designed macrocyclic hosts. Ref. 3a, 1987, **3**, 337–419
9 Vögtle, F. and Müller, W.M. Complexation of neutral guests within cavities of synthetic neutral host molecules. *J. Incl. Phenom.* 1984, **1**, 369–386
10 Weber, E. and Josel, H.–P. A proposal for the classification and nomenclature of host-guest-type compounds. *J. Incl. Phenom.* 1983, **1**, 79–85
11 Weber, E. Clathrate chemistry today — Some problems and reflections. Ref. 3e, 1987, **140**, 1–20
12 MacNicol, D.D. and Wilson, D.R. New strategy for the design of inclusion compounds: Discovery of the 'hexa-hosts'. *J. Chem. Soc., Chem. Commun.* 1976, 494–495
13 Vögtle, F., Löhr, H.G., Puff, H. and Schuh, W. Ein neuartiger Typ ionischer Clathranden für zahlreiche Einschlußverbindungen. *Angew. Chem.* 1983, **95**, 425–426; *Angew. Chem., Int. Ed. Engl.* 1983, **22**, 409
14 Weber, E., Csöregh, I., Stensland, B., and Czugler, M. A novel clathrate design: selective inclusion of uncharged molecules via the binaphthyl hinge and appended co-ordinating groups, X-ray crystal structures and binding modes of 1,1'-binaphthyl-2,2'-dicarboxylic acid host/hydroxylic guest inclusions. *J. Am. Chem. Soc.* 1984, **106**, 3297–3306
15 Hart, H., Lin, L.T.W. and Ward, D.L. Molecular design for hosts in crystalline host-guest complexes. *J.Am. Chem. Soc.* 1984, **106**, 4043–4045
16 Toda, F., Tanaka, K., Hyoda, T. and Mak, T.C.W. Design of a new host compound, 2,2-di(p-hydroxyphenyl)propane, and crystal structure of its 1:1 complex with methylhydrazine. *Chem. Lett.* 1988, 107–110
17 Weber, E. and Czugler, M. Functional group assisted clathrate formation — scissor-like and roof-shaped host molecules. Ref. 3e 1988, **149**, 45–135
18 Csöregh, I., Czugler, M., and Weber, E. (unpublished results)
19 Weber, E., Csöregh, I., Ahrendt, J., Finge, S. and Czugler, M. Design of roof-shaped clathrate hosts. Inclusion properties and X-ray crystal structures of a free host and of inclusion compounds with 1-BuOH and DMF. *J. Org. Chem.* 1988, **53**, 5831–5839
20 Csöregh, I., Czugler, M. and Weber, E. Structural studies of the inclusion properties of a novel coordinatoclathrate host. *Molecular Structure: Chemical Reactivity and Biological Activity*, Stezowski, J.J., Huang, J.L., Shao, M.–C (Eds.). International Union of Crystallography, Oxford University Press, 1988, 390–395
21 Czugler, M., Weber, E. and Ahrendt, J. Selective clathrate formation with the new host system cis- and trans–9,10-dihydro-9,10-ethanoanthracene-11, 12-dicarboxylic acid: Inclusion properties and X-ray structure of an encapsulated acetic acid dimer. *J. Chem. Soc. Chem. Commun.* 1984, 1632–1634
22 (a) Rebek, Jr. J. Model studies in molecular recognition. *Science* 1987, **235**, 1478–1484. (b) Rebek, Jr. J. Recent progress in molecular recognition. Ref. 3e 1988, **149**, 189–210
23 Gartland, G.L., Freeman, G.R. and Bugg, C.E. Crystal structures of tryptamine picrate and D, L-tryptophan picrate-methanol, two indole donor-acceptor complexes. *Acta Crystallogr.* 1974, **B30**, 1841–1849
24 Weber, E., Hecker, M., Csöregh, I. and Czugler, M. New host family based on small-ring compounds. (submitted for publication)
25 Cf. Kamiya, K., Takamoto, M., Wada, Y. and Asai, M. Structure of sulfazecin-methanol (1/1). *Acta Crystallogr.* 1981, **B37**, 1626–1628
26 Huggins, M.L. 50 Jahre Theorie der Wasserstoffbrückenbindung. *Angew. Chem.* 1971, **83**, 163–168; *Angew. Chem., Int. Ed. Engl.* 1971, **10**, 147
27 Taylor, R. and Kennard, O. Crystallographic evidence for the existence of C–H···O, C–H···N, and C–H···Cl hydrogen bonds. *J. Am. Chem. Soc.* 1982, **104**, 5063–5070
28 Czugler, M., Stezowski, J.J. and Weber, E. Co-ordination-assisted inclusion of neutral molecules by the racemic 9,9'-spirobifluorene-2,2'-dicarboxylic acid host lattice. X-ray crystal structure of the dimethylformamide clathrate at 170K. *J. Chem. Soc., Chem. Commun.* 1983, 154–155
29 Csöregh, I., Sjögren, A., Czugler, M., Cserzö, M.

and Weber, E. Versatility of the 1,1′-binaphthyl-2,2′-dicarboxylic acid host in solid-state inclusion: Crystal and molecular structure of the dimethylformamide (1:2), dimethyl sulfoxide (1:1), and bromobenzene (1:1) clathrates. *J. Chem. Soc., Perkin Trans. 2*, 1986, 507–513

30 Weber, E., Hecker, M., Koepp, E., Orlia, W., Czugler, M., and Csöregh, I. New trigonal lattice hosts: Stoicheiometric crystal inclusions of laterally trisubstituted benzenes—X-ray crystal structure of 1,3,5,-*tris*-(4-carboxyphenyl)benzene·dimethylformamide. *J. Chem. Soc., Perkin Trans. 2*, 1988, 1251–1257

31 Csöregh, I., Czugler, M., Ertan, A., Weber, E. and Ahrendt, J. Solid-state binding of dimethyl sulphoxide involving carboxylic host molecules. X-ray crystal structures of four inclusion species *J. Incl. Phenom.* 1989, 7, (in press)

32 Allen, G. and Caldin, E.F. The association of carboxylic acids. *Quart. Rev.* 1953, 7, 255–278

33 Leiserowitz, L. Molecular packing modes. Carboxylic acids. *Acta Crystallogr.* 1976, **B32**, 775–802

34 Csöregh, I., Czugler, M., Weber, E., and Ahrendt, J. Formation of isolated guest dimers vs. host-guest coordination. X-ray crystal structures of four carboxylic acid inclusion compounds by roof-shaped and scissor-like host molecules *J. Incl. Phenom,* 1989, 7 (in press)

35 Weber, E., Finge, S. and Csöregh, I. (unpublished results)

36 Etter, M.C. Aggregate structures of carboxylic acids and amides. *Isr. J. Chem.* 1985, **25**, 312–319

37 (a) *Organic Solid State Chemistry (Studies in Organic Chemistry, Vol. 32)*, Desiraju, G.R. (Ed.). Elsevier, Amsterdam, New York, 1987. (b) *Organic Chemistry in Anisotropic Media (Symposia-in-Print, Number 29)*, Scheffer, J. (Ed.) *Tetrahedron*, 1987, **43**, 1197–1745

38 (a) Williams, D.J. Organische polymere und nichtpolymere Materialien mit guten nichtlinearen optischen Eigenschaften. *Angew. Chem.* 1984, **96**, 637–651; *Angew. Chem., Int. Ed. Engl.* 1984, **23**, 690. (b) *Nonlinear Optical Properties of Organic Molecules and Crystals, Vols. 1 and 2*, Chemla, D., Zyss, J. (Eds.). Academic Press, New York, 1987

39 Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed. VCH Verlagsgesellschaft, Weinheim, 1988, 51

40 Toda, F. Isolation and optical resolution of materials utilizing inclusion crystallization. Ref. 3e 1987, **140**, 43–69

41 Weber, E., Dörpinghaus, N. and Goldberg, I. Selective clathrate inclusion of primary and secondary amines in a new host series. Crystallographic reasoning of the inclusion behaviour. *J. Chem. Soc., Chem. Commun.* 1988, 1566-1568

Functional Group Assisted Clathrate Formation — Scissor-Like and Roof-Shaped Host Molecules

Edwin Weber[1] and Mátyás Czugler[2]

1 Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Straße 1, D-5300 Bonn-1, FRG
2 Central Research Institute of Chemistry
Hungarian Academy of Sciences, Pusztaszeri út 59–67
H-1025 Budapest, Hungary

Table of Contents

1 The Starting Observation 47

2 Functional Group Assisted Clathrate Formation 47
2.1 An Old Matter or a Missing Event? 47
2.2 Nature of the Concept (Coordinatoclathrate Concept) and Basic Host Design 51

3 Suggested Coordinatoclathrate Hosts and Chemical Proving of the Concept 53
3.1 General Considerations 53
3.2 1,1'-Binaphthyl-2,2'-dicarboxylic Acid (*1*) — The Initial Touchstone . . . 55
3.2.1 Structural Relation to a Pair of Scissors 55
3.2.2 Formation of Inclusion Compounds, Host-Guest Stoichiometries 56
3.2.3 Stabilities and Decomposition Properties of the Crystal Inclusions 58
3.2.4 Guest Selectivity Behavior, Separation of Solvent Mixtures 58
3.3 Scissor-like Host Molecules Having Altered Building Blocks 60
3.3.1 Examples of Selected Compounds 60
3.3.2 Inclusion Properties 62
3.4 Host Molecules Related to a Roof 65
3.5 Analogues Lacking Functional Groups and Related Compounds 71

4 Proving the Concept by X-Ray Crystallography 76
4.1 Structures of Free Host Molecules 78
4.2 Function of Sensor Groups in Binding Guest Molecules 80
4.2.1 Inclusion Compounds Involving Readily Deprotonizable (Proton-Donating) Guest Molecules: Alcohols and Acids as Guest Species 80
4.2.2 Inclusion Compounds Involving Readily Protonizable (Proton-Accepting) Guest Molecules: Salt-type Associates and Ternary Complexes of *7* and Imidazole Clathrate of *13* 89
4.2.3 Inclusion Compounds Involving Aprotic-Dipolar Guest Molecules: Dimethylformamide and Dimethyl Sulfoxide as Guest Species . . . 92

Topics in Current Chemistry, Vol. 149

4.3 Inclusion Compounds Without Specific Binding Contacts Between Host and Guest: Apolar Molecules as Guest Species 100
4.4 Cavity Shapes: Steric Fit of Host-Guest Compounds 103
4.5 Interrelations Attributable to Special Host and Guest Features 109
4.5.1 Shape and Symmetry Considerations: Dihedral Angles of Host Compounds 109
4.5.2 Effects Due to the Amphiphilic Nature of Host Compounds . . . 117
4.5.3 Stoichiometry and Other Thermodynamics-Related Effects 118

5 Coordinatoclathrates in Active Site Modelling of Protease Enzymes: Associates of *1* with Imidazole 119
5.1 Crystalline Associate of *1* with Imidazole and Water (1:1:2) [*1* · Im · 2 H_2O] 120
5.1.1 Intra-associate Relations in *1* · Im · 2 H_2O 120
5.1.2 Inter-associate (Packing) Relations in *1* · Im · 2 H_2O 121
5.1.3 Structural and Electrostatic Similarity of *1* · Im · 2 H_2O to Serine Protease Enzymes 123
5.1.4 Water-Mediated Proton Transfer 125
5.2 Crystal Structure of the Anhydrous 1:1 Associate of *1* with Imidazole [*1* · Im] 126
5.2.1 Intra-associate Relations in *1* · Im (1:1) 126
5.2.2 Packing and Energy Relations in *1* · Im (1:1): Structural Model for Logic Circuits at the Molecular Level 127

6 Conclusions and Prospects 128

7 Acknowledgements 130

8 References 130

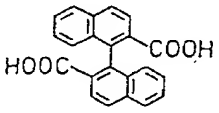
A strategy has been developed for the design, synthesis, and testing of new clathrate hosts that possess relationship complementarity to specific guest-compounds.

The new approach starts from particular host geometries (related to scissors or a roof) and makes extensive use of functional group interactions between host and guest molecules allowing planned inclusion properties. Functional sensor groups are characterized as H-bond donors and/or acceptors of different strength. The crystalline supramolecular systems formed in this way are members of the new type of "coordinatoclathrates" (coordinative group assisted clathrates) which usually are more stable than the conventional clathrates. They form highly selectively, and are predictable within certain limits. Also, they provide insight into the elementary interactions of functional groups on which molecular recognition is generally based. For comparative studies, the corresponding apolar host analogues typical of van der Waals interactions are covered as well.

The article is devided into sections which put the emphasis of discussion either on chemical (Sects. 1–3) or on crystallographic aspects (Sect. 4). Section 5 shows points of contact between coordinatoclathrate formation and biochemical problems.

1 The Starting Observation

The outset was an observation by chance concerning 1,1'-binaphthyl-2,2'-dicarboxylic acid (*1*). This compound, when obtained by the common procedure[1], gave an amorphous powder, but when crystallized from ethanol, resulted in colorless transparent crystals [2]. The crystals contain solvent which is retained very strongly in the lattice and resists drying conditions, e.g. vacuum (15 Torr) at room temperature, without appreciable decomposition [3]. Forced drying conditions (0.1 Torr, raised temperature) are required to decompose the adduct, while at ambient conditions it is storable and stable for nearly an unlimited time. From elemental analysis, it follows that two moles of ethanol correspond exactly to one mole of the acid [2]. These observations suggest the presence of a clathrate [4–6] (crystal lattice inclusion, cf. Chapter 1 in Vol. 140 of this series, 'Molecular Inclusion and Molecular Recognition — Clathrates I') where the characteristic groups (carboxyl and hydroxyl) are



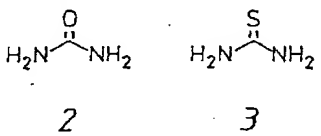
1

important, e.g. assisting the host-guest binding coordinatively; a stimulus to reflect on it.

2 Functional Group Assisted Clathrate Formation

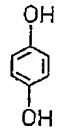
2.1 An Old Matter or a Missing Event?

Polar and coordinatively active functional groups are structural elements frequently found in the constitution of crystal inclusion hosts, mainly including conventional host molecules [7]. Typical examples are urea (*2*), thiourea (*3*), hydroquinone (*4*), Dianin's compound (*5*), deoxycholic acid (*6*) or simply water (Fig. 1). This was the reason to assume that functional groups play an important part in the construction of crystal inclusion compounds.

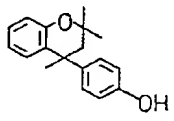


2

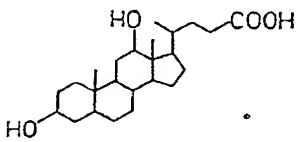
3



4



5



6

Fig. 1. Constitutions of well-known clathrate (lattice inclusion) hosts equipped with polar (H-bond-active) functional groups

Ordinary tetragonal urea (*2*), e.g. on crystallization from appropriate solvents forms a hexagonal non-close-packed crystal lattice which shows long "infinitely" extended channels. They are apt to accommodate solvent molecules or other organic species matching the channel dimensions (e.g. unbranched hydrocarbons) [9–11]. Actually this particular inclusion behavior is an unexpected fact for a molecule with such a low molecular weight (M = 60.0). Looking at the inclusion structures [11], the reason becomes quickly obvious. Figure 2 shows for a n-alkane inclusion compound that the urea molecules form a specific H-bridge network, at which each oxygen is bound to four nitrogen atoms, and each nitrogen to two oxygen atoms of adjacent urea molecules [12]. H-bonds are also responsible of the helical grouping of the urea molecules in the channel wall and thus for the helicity of the respective inclusion lattice [6]. Contribution to a direct binding of guest molecules in the channel interior via H-bonds occurs, however, only in very exceptional cases. There are van der Waals forces well to the fore.

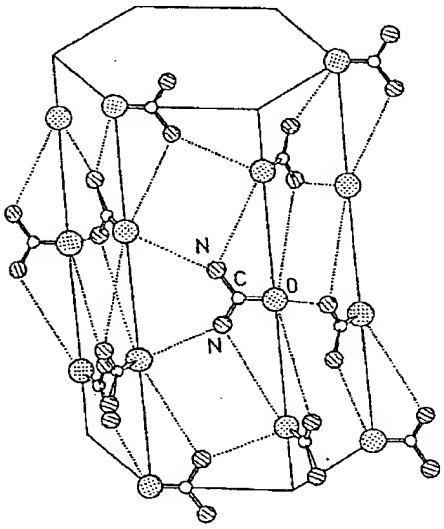


Fig. 2. The H-bonded hexagonal channel network of urea (*2*) typical for a *n*-hydrocarbon inclusion compound (H-bonds as dotted lines) (Adapted from Ref. 12)

A similar behavior is found for thiourea (*3*), except for the channel diameter which is expanded (from 5.25 for urea to 6.1 Å for thiourea); consequently there is enough space available to accommodate more voluminous guest compounds, e.g. branched hydrocarbons [11].

Also deoxycholic acid (*6*) crystallizes in an inclusion lattice with channel-shaped cavities [13]. Figure 3 shows that they are formed by facing molecules of deoxycholic acid [14]. This characteristic structural unit is a double layer of head-to-tail linked deoxycholic acid molecules at which specific H-bridges between hydroxy and carboxy groups are the decisive fact. The channels as such (e.g. in case of the orthorhombic crystal, see Fig. 3) are lined with lipophilic groups. Thus only van der Waals contacts are kept between the included guest molecules (also for polar molecules like acetone, Fig. 3) and the molecules of the channel wall.

In the crystal inclusion compounds of the phenols, e.g. of hydroquinone (*4*) or of

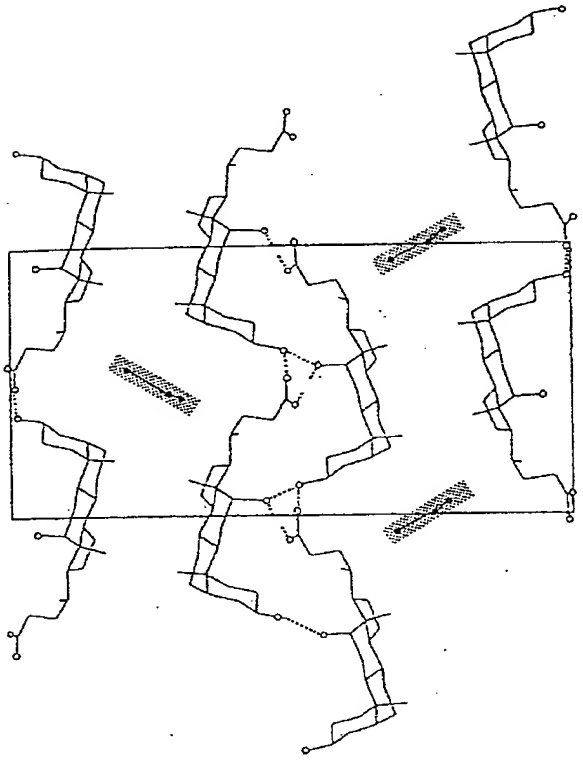


Fig. 3. Channel inclusion compound of deoxycholic acid (6) with acetone. The crystal packing is affected by head-to-tail H-bond-mediated double layers of host molecules (H-bonds as dotted lines, guest molecules shaded) (Adapted from Ref. 13)

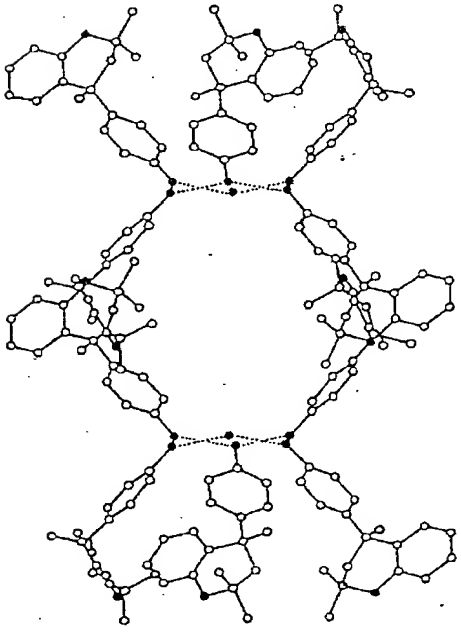


Fig. 4. Inclusion cage of Dianin's compound (5). The matrix is constructed via a cyclic H-bonded hexagonal system of host molecules (on top and on bottom of the macrocage; O atoms as bold dots, H-bonds as dotted lines); bulky parts of the host molecules interlock (equatorial of the cage). The cage can be filled with molecules of fitting size (e.g. one molecule of chloroform) (Adapted from Ref. 16)

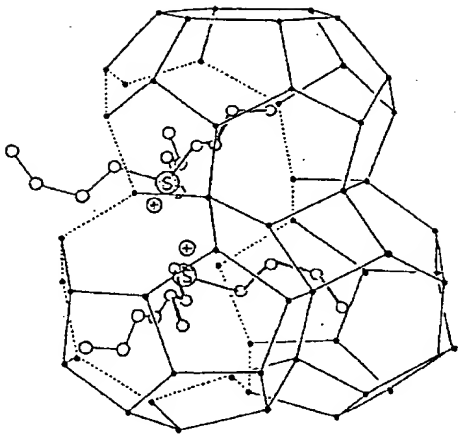


Fig. 5. Constitution of a typical hydrate clathrate (tri-n-butylsulfonium ion as guest). The guests are accommodated within H-bond-mediated water polyhedrons (apexes are equivalent to water oxygens) (Adapted from Ref. 6)

the Dianin's compound (*5*), the hydroxy groups are used to construct hexagonal cyclic H-bridge systems [15,16]. In case of the Dianin's compound (Fig. 4), cages in the crystal lattice are created, having a diameter of approx. 6.2 Å, where spatially fitting molecules from different classes of compounds can be included [16]. The host lattice acts as a sterical barrier.

The same applies to the historic gas-hydrates (hydrate clathrates, Fig. 5) [17,18]. However, on principle, only such molecules are suited for inclusion into the complicated H-bridge networks of gas-hydrates which do not interfere with the H-bridges of water, but have a hydrophobic nature. More recent hosts related to this inclusion principle are given in Chapter 3 of this book.

The examples might have illustrated that functional groups (e.g. OH, COOH, NH_2), as they are a component of classical crystal inclusion compounds[4-7], are usually used for construction, cross-linking, and stabilization of the host lattice (Fig. 6a), and are not used, as could have been, for direct binding of guest molecules, e.g. via coordination or H-bonding (Fig. 6b). To speak with a newly developed classification system on inclusion compounds [19] (see Chapter 1 of Vol. 140), those are "true" clathrates and not "coordinatoclathrates" (cf. Fig. 6, for a more detailed specification see Fig. 15 in Chapter 1 of Vol. 140). As in the case of urea and thiourea, a rather stable, but nearly invariable host lattice with rigidly

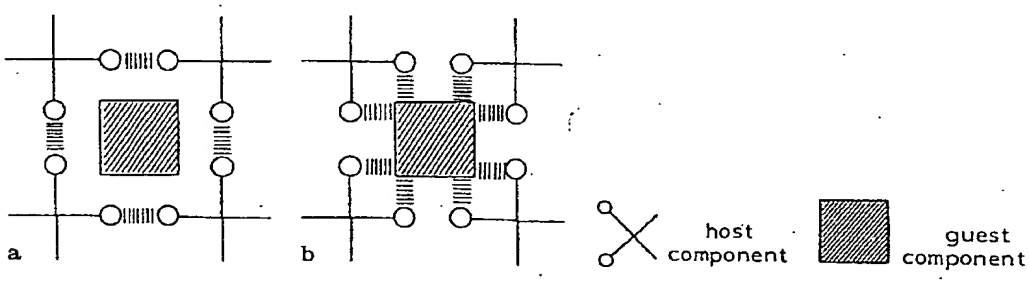


Fig. 6. Diagrammatic (two-dimensional) representation of different modes of lattice inclusions involving coordinative (H-bond) interactions (indicated by broken lines): (a) cross-linked matrix type of inclusion (host-host interaction, "true" clathrate); (b) coordinatoclathrate type of inclusion (coordinative host-guest interaction, coordination-assisted clathrate)

definite cavity dimensions results. That is why the chemical nature of inclusion partners in case of such crystal compounds (with exception of gas hydrates) generally play only a minor part. Whether a molecule is included or not, depends at first approximation on its size and shape (guest selection by molecular size and shape). Examples, deviating from this observation, are rarely found in the literature before 1984 or show no general principle [20]. To define such a principle is subject of the following section.

2.2 Nature of the Concept (Coordinatoclathrate Concept) and Basic Host Design

It is commonly accepted [21] but unwritten law: bulkiness and crystal inclusion are closely related. In Figs. 2–5 (Sect. 2.1) this principle is confirmed by bulky cross-linking of actually non-bulky host molecules, e.g. using polar groups ("bulky crystal network"). By way of contrast, we aim at transferring the element of bulkiness into the host skeleton ("molecule inherent bulkiness") and use the polar groups differently, e.g. for direct guest binding. This is the basic tenor of the new strategy and serves as a general definition regarding former reflections (cf. hydroquinone). A more detailed description is given below.

The origin of the strategy of "*coordinatoclathrate inclusion*" was the desire to get hold of more, and above all, more highly effective tools for specific host/guest adjustment [22]. As mentioned above, conventional clathrate inclusion formers (see Fig. 1), and in addition many host-compounds of recent date, are mainly qualified to select guest molecules according to size and shape. Imagine a mixture of molecules with comparable dimensions, but belonging to different classes of substances (e.g. acetone, isopropanol, 2-chloropropane), they should possibly be selected by chemical aspects, too.

Beside a crystal cavity of suitable size, additional information is required, e.g. designed polarity gradients in the cavity or carefully located and specific binding sites, respectively. At best, the crystal inclusion will enjoy an ideal "lock and key" relation [23] between host and guest components from a chemical and spatial point of view.

The latter could be obtained, if particular donor substituents (e.g. specific functional groups) facing corresponding acceptor groups of the guest molecule are added to the host and vice versa, thus using specific host-guest interactions of polar

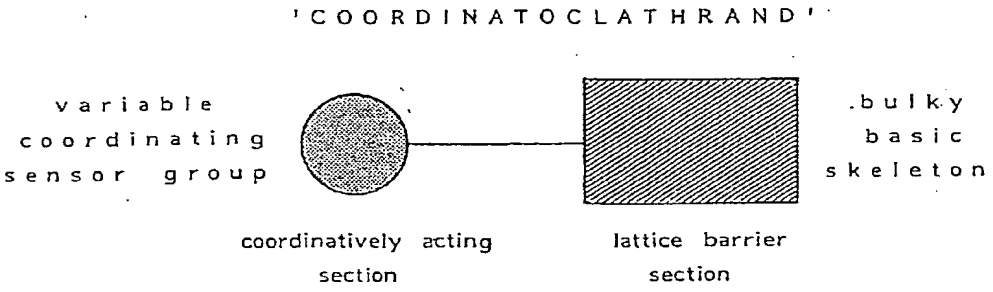


Fig. 7. Abstracted structure of a host molecule characteristic of coordinatoclathrate formation [2]

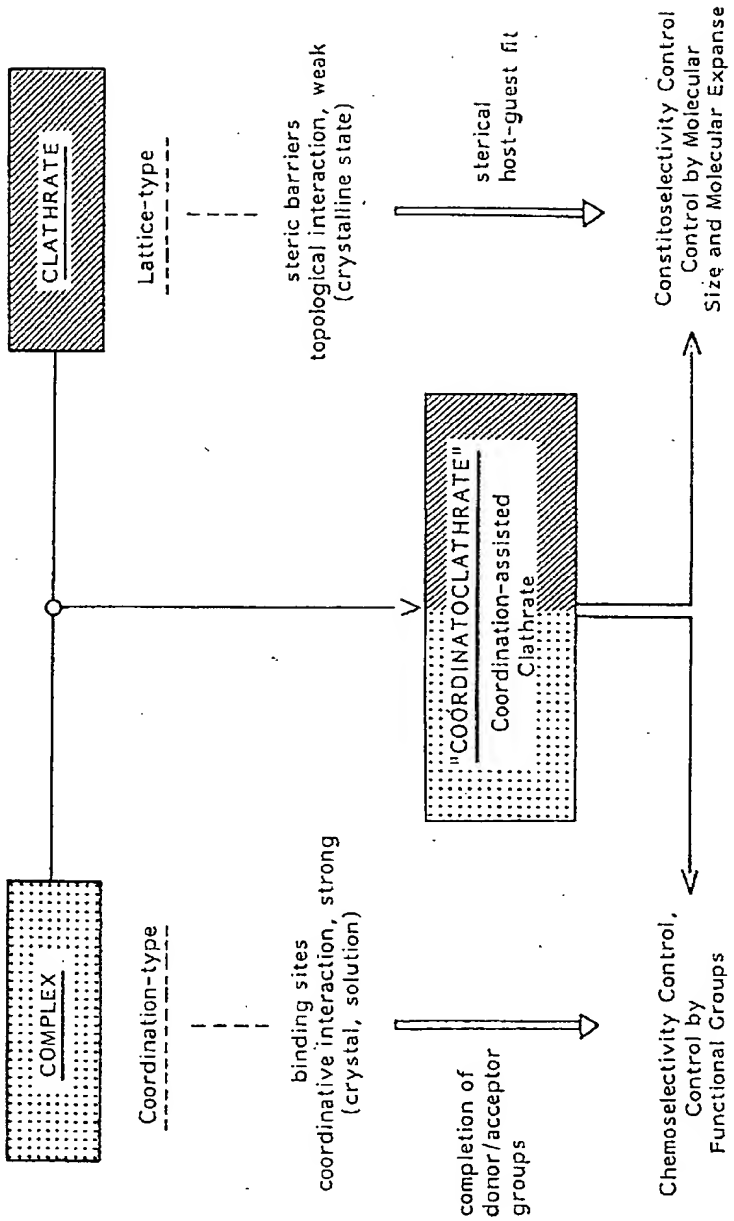


Fig. 8. Coordinatoclathrate concept: definitions, relations, and functions of control [2]

nature such as dipol-dipol attraction or H-bonds at guest selection [24] (see Fig. 6). Basic problems are to prevent or to disguise interactions with molecules of the same kind, i.e. host with host or guest with guest. This is not trivial, since many polar groups (e.g. C—OH, COOH etc.) are simultaneously donors and acceptors. Consequently high inclusion selectivities depend on a very precise selection and balance of polar and functional groups in the host-guest unit. Here, bulky parts of the molecular framework are important. They are required to construct cavities, i.e. non-close-packed host lattices (see above), but also to prevent the polar groups of the individual host molecules from contacting one another undisturbed, i.e. satisfying themselves.

Accordingly the most important feature of a host compound designed for coordinatoclathrate formation [2] is a bisection in the molecule, as schematically shown in Fig. 7, providing:

1) a *bulky basic skeleton* which makes the clathrate-typical lattice cavities available,
2) *appended functional groups (sensor groups)* which manage the coordination to the included guest substrate.

Combining features typical of both complexes and clathrates (coordinatoclathrate) should provide new possibilities of host-guest control [2]. They are indicated by the relations specified in Fig. 8, e.g. chemoselectivity or selectivity for functional groups on the one hand, caused by the complex part, and on the other hand constitutional selectivity or selectivity for molecular size and expanse due to the clathrate branche of the diagrammatic family tree of a coordinatoclathrate shown in Fig. 8.

Another advantage of using oriented polar and coordinative bonds between the host and the guest molecule, as is intended by the coordinatoclathrate principle, is facilitation of lattice design. Moreover, it is assumed that a possible coordinatoclathrate inclusion, because of the relatively strong binding forces (dipole-dipole attraction, H-bridges) [24] acting in the host-guest unit, involves little disorder and higher stability than conventional-type clathrates for which weak van der Waals interactions in the crystal aggregates are more typical [25] (cf. Sect. 2.1). It is important to give the hereby shown strategy a background based on molecules.

3 Suggested Coordinatoclathrate Hosts and Chemical Proving of the Concept

3.1 General Considerations

The "coordinatoclathrate principle" is intended for host molecules endowed with both a bulky basic skeleton and appended sensor groups. This design of a general structure requires some differentiations.

Molecules aim at being packed as closely as possible in the crystal [26–28]. *Bulkiness* of a molecule, however, is an impediment. It presupposes a molecular constitution rather unbalanced in its spatial dimensions and a certain extent of conformational rigidity. Here we encounter a parallel to an everyday occurrence: trunks can easily be arranged to a compact ordered stack, unlike bulky root stocks which cannot. The

latter, by contrast, yield a relatively disordered, labile stack interspersed with voids. The same holds for molecules.

Here, however, it is possible to obtain stabilization of the low-dense lattice build-up of bulky molecules via intermolecular adhesion and orientation forces. Molecules with planar structural elements are advantageous in this respect since they are apt to support the lattice aggregate, and at the same time they are able to partition off cavities effectively. It is very convenient to use aromatic units.

Figure 9 goes more deeply into these considerations. The geometric figure (A) which is obtained by cross-connection of two plane subunits is representative of a bulky molecule. There are several possibilities of arranging these molecules in a two-dimensional pattern (top view), e.g. two terminals of the cross-shaped molecules in each case are in contact giving a molecular packing of particularly low density (a) (free space shaded), or (b), (c), and others where the free space is further subdivided and modified. How the host molecules are arranged (a–c) depends on the polarity conditions, e.g. whether hydrophilic or hydrophobic terminals or regions of the molecules touch.

Figure 10 where some facts are assumed in respect to molecular polarity and the type of arranging the molecules explains that the lattice cavities are not of uniform chemical nature, but are subdivided in polar (broken circles) and apolar regions (continuous circles). On possible inclusion of guest molecules, the guest will be oriented according to the polarity gradient, or interact coordinatively with the host lattice ("coordinatoclathrate principle"). Considered in three dimensions, a decisive factor is, whether a newly added layer of molecules arranges in a congruent or a shifted position. In the former case channels, in the latter case cavity-type voids are created in the respective crystal lattice.

Evidently, *symmetry attributes* of the host (and guest) molecules play also a role in these considerations [26,29]. We prefer to design host molecules by using a two-fold symmetry element [30]. A direct connection between host symmetry and the coordinatoclathrate principle, however, does not necessarily emerge from the given statement, though, of course, symmetry conformity of host and guest molecules are general parameters of selection.

Concerning the *nature of the sensor groups* at the host molecule, one should aim at binding contacts to the corresponding guest molecule as selective and strong as possible. Functional groups qualified as H-bond mediators meet the requirements

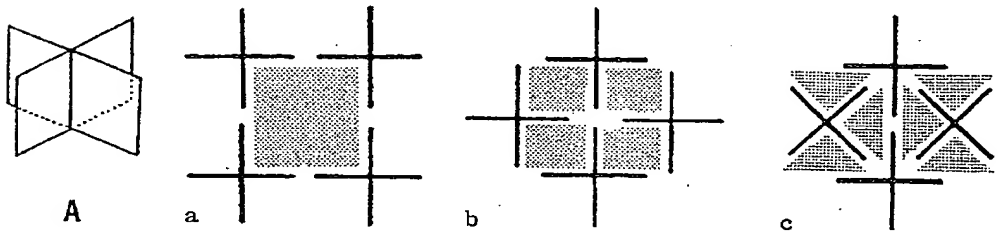


Fig. 9. Diagrammatic representation of a bulky host constitution (A) and (a)—(c) of crystal lattice-analogous arrangements of A (two-dimensional versions; shaded areas represent the lattice voids)

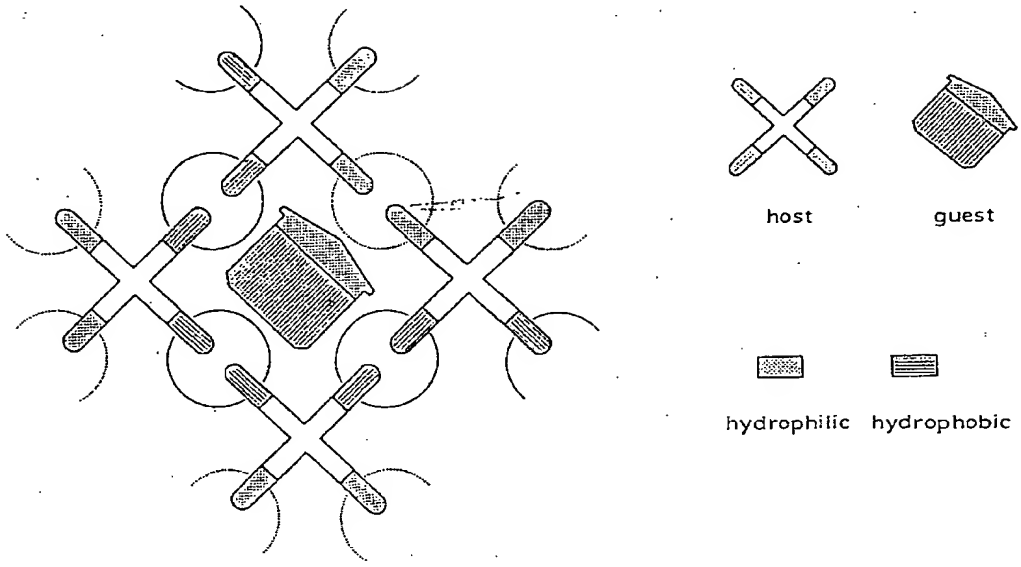


Fig. 10. Relation between amphiphilic nature and orientation of crystal lattice and guest. Hydrophilic and hydrophobic interactions are indicated by circles in dotted and non-interrupted style of line representation, respectively

best. Thus, different OH-, NH-, CO-groups, and other functionalities containing heteroatoms are suitable behaving either like H-donors or H-acceptors, or both at the same time.

Within the limits of this article, we attached importance to keeping the range of the used sensor groups easy to survey and to limiting variation in respect to the bulky basic skeleton to only a few selected structures which are closely connected with the geometric figure shown in Fig. 9, i.e. molecules shaped like scissors or roofs.

3.2 1,1′-Binaphthyl-2,2′-dicarboxylic Acid (*1*) — The Initial Touchstone

3.2.1 Structural Relation to a Pair of Scissors

A common pair of tailor's scissors (Fig. 11 a) has the twofold symmetry (C_2) we prefer. On opening the edges, the scissors gain bulkiness. One can say a pair of scissors is "polar", too. One part serves for cutting, the other for handling.

It is possible to translate the symbolism of the scissors and its basic structure into the field of molecules (cf. Fig. 11 b). Indeed, the scissor-shaped bulky binaphthyl compound equipped with two appending carboxy groups *1* (1,1′-binaphthyl-2,2′-dicarboxylic acid, Fig. 11 c), as mentioned at the beginning (Sect. 1), strictly meets the general structure of an assumed coordinatoclathrate host (cf. Fig. 7). Also, the compound is in keeping with the considerations on an expectedly favorable lattice build-up (see Sect. 3.1). For checking, the crystal inclusion properties of *1* were studied in detail [2].

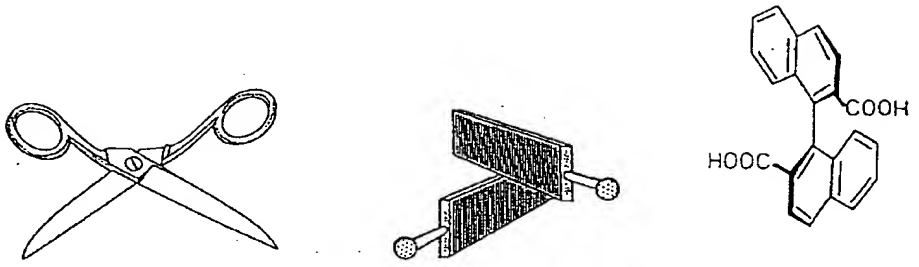


Fig. 11. Graphic development (a)–(c) of a molecular constitution (coordinatoclathrate host *1*) compared to a pair of scissors

3.2.2 Formation of Inclusion Compounds, Host-Guest Stoichiometries

The question arises, whether and to what extent the dicarboxylic acid *1* is capable of binding other solvents besides ethanol (starting observation, cf. Sect. 1) in the crystal lattice. For this purpose, to begin with, crystallization experiments using further alcohols (straight-chain, branched, univalent and polyvalent) were carried out. It was found that *1* is apt to form crystal inclusions on a large scale, i.e. with alcohols of various constitutions. A list of different examples is given in Table 1 (Entries 1–16).

It is important to note that, depending on the spatial requirements of the used alcohol and on the number of hydroxyl groups existing in the alcohol, different stoichiometries (*1*:alcohol) predominate in the crystal lattice. For instance, methanol (Entry 1) and ethanol (Entry 2) are accommodated in the crystal of *1* with 1:2 stoichiometry, whereas the isomeric butanols (Entries 5–8) give rise to 1:1 stoichiometry. The same holds for the inclusions of benzyl alcohol (Entry 13) and of trichloroethanol (Entry 14) as bulky guest substitutes and for those of the bifunctional representatives ethylene glycol (Entry 15) and propylene glycol (Entry 16).

Since H-bonding as a supporting factor for inclusion formation seemed very likely, one passed over to solvents having a very high potency for proton donorship. In this context it was found that carboxylic acids have also an affinity to intercalate into the lattice of *1*. Examples belonging to this sort of host-guest inclusion were obtained for acetic, propionic, and lactic acids (Entries 17–19); the stoichiometries vary from 2:3 to 2:1. But also in the area of carboxylic acid derivates free of hydroxyl, by preference amides, many fewer esters which are suitable partners for inclusion formation are found. For instance formamide, N-methylformamide, and N,N-dimethylformamide (Entries 20–22) all led to inclusions with 1:2 (host:guest) stoichiometry, whereas the host-guest aggregates formed with esters, e.g. dimethyl carbonate or diethyl carbonate (Entries 23 and 24), gave no reproducible stoichiometry ratio after drying under usual conditions (cf. Table 1) because of their low stability.

On the other hand, CH-acidic solvents such as acetylacetone, acetonitrile, nitromethane, and dimethyl sulfoxide (Entries 25–28) yield stable crystal inclusions, each having a strict 1:1 stoichiometry. Finally, respective crystallization experiments using solvents of even less polarity or ability to form H-bonds have been carried out. The

Table 1. Clathrate inclusion compounds of *1*: stoichiometries and thermal stability characterization

Entry	Guest compound	Host:guest mol ratio[a]	Thermal dec [°C][b]
1	methanol	1:2	146 (+82)
2	ethanol	1:2	88 (+10)
3	1-propanol	2:1	72 (—25)
4	2-propanol (isopropanol)	1:2	86 (+ 4)
5	1-butanol	1:1	72 (—46)
6	2-butanol (sec-butanol)	1:1	92 (— 7)
7	2-methyl-1-propanol (isobutanol)	1:1	71 (—37)
8	2-methyl-2-propanol (t-butanol)	1:1	141 (+58)
9	1-pentanol	1:2	123 (—15)
10	2-methyl-1-butanol	2:1	135 (+ 7)
11	2-methyl-2-butanol	1:2	164 (+62)
12	4-methyl-1-pentanol	1:1	154 (— 9)
13	benzyl alcohol	1:1	120 (—85)
14	trichloroethanol	1:1	117 (—34)
15	ethylene glycol	1:1	165 (—32)
16	propylene glycol	1:1	149 (—66)
17	acetic acid	2:3 (1:1)	115 (— 3)
18	propionic acid	2:1	139 (— 2)
19	lactic acid	1:1	140 (—)[e]
20	formamide	1:2	136 (—74)
21	*N*-methylformamide	1:2	108 (—75)
22	*N,N*-dimethylformamide (DMF)	1:2	117 (—35)
23	dimethyl carbonate	2:1[c]	<25
24	diethyl carbonate	[d]	<25
25	acetylacetone (2,4-pentanedione)	1:1	64 (—70)
26	acetonitrile	1:1	119 (+38)
27	nitromethane	1:1	126 (+25)
28	dimethyl sulfoxide (DMSO)	1:1	155 (—34)
29	diethyl ether	[d]	<25
30	bromobenzene	1:1	116 (—40)

[a] Determined by NMR integration after a drying period of 12 h at 0.5 torr for each compound. [b] Value indicates the beginning of the clathrate decomposition (either onset of opacity or release of the gaseous component). Specification in parentheses gives the relative thermal stability (difference between the decomposition point of the clathrate and the boiling point of the respective neat guest solvent at atmospheric pressure). [c] Decomposes under vacuum drying at ambient temperature. [d] Unstable at atmospheric pressure. [e] No description of the boiling point for the neat guest solvent in the literature.

results show that attractive powers emanating from such solvent components are, as a rule, insufficient to form a stable inclusion aggregate. We were just able to isolate a 1:1 stoichiometric inclusion compound of the relatively non-polar, but difficultly vaporizable bromobenzene (Entry 30), whereas diethyl ether as a guest component seems too volatile to be retained in the host lattice under ambient conditions [2].

Amines are expected to form a salt in contact with *1*. For the present, compounds like amines have generally been regarded as less suitable guest components. Nevertheless, highly interesting conditions were found in case of the aggregate where *1*, imidazole, and water are combined in a single crystal lattice. The special features of this inclusion aggregate are reported separately (Sect. 5.1).

3.2.3 Stabilities and Decomposition Properties of the Crystal Inclusions

With some exceptions, the isolated crystal inclusion compounds are almost indefinitely stable under ambient conditions (cf. Table 1) and allow storage in air over a long period with no appreciable decomposition [2]. Also under vacuum conditions (0.5 Torr, 12 h, 25 °C) the majority of the inclusion compounds, being discussed here, exhibit a remarkably strong guest fixation (cf. Sect. 1). Only on heating (under reduced pressure, 0.5 Torr), a decomposition with growing opacity of the formerly transparent crystals or with spontaneous bursting of the crystal and evolution of a gas is observed within a specific temperature range for each compound (Table 1).

In the case of the methanol, ethanol, t-butanol, 2-methyl-2-butanol, acetonitrile, and nitromethane inclusion compounds (Entries 1, 2, 8, 11, 26, and 27 in Table 1), these temperature ranges lie above the boiling point of the corresponding guest solvent (cf. values given in parentheses in Table 1). It is shown most remarkably by methanol, for which the boiling point and the point for the beginning of the decomposition differ by 70 °C. This indicates a particularly strong clathration (e.g. comparable to the corresponding tri-o-thymotide solvent inclusion which is representative of high thermal stability and strong clathration [31]. For the bulk of the isolated inclusion compounds, however, the decomposition point falls rather into the range of the boiling point of the corresponding pure guest component or just below. It may illustrate a way to distinguish between thermally stable and less stable inclusion compounds.

IR spectra (KBr) of the crystalline inclusion compounds highlight bands which document a coordinative host-guest interaction in accordance with our concept. The values for the OH-stretching modes of the lattice-included alcohols, e.g. indicate strong H-bridge bonding as they are very close to those found in the pure liquid alcohols rather than of the alcohols in the gaseous state (e.g. 3374 in the lattice-included species versus 3676 cm^{-1} for gaseous ethanol) [32]. The absorptions in the 1700 cm^{-1} region arising from the carbonyl groups of the host molecule, as expected, suggest stronger interactions in the alcohol cases than in the others. Results of solid-state NMR measurements (^{13}C—CP-MAS spectra) are not relevant to the problem, at least for the time being.

3.2.4 Guest Selectivity Behavior, Separation of Solvent Mixtures

If mixtures of two or more potential guest molecules are offered, the host lattice of *1* allows the selective accommodation of solvent molecules [2]. In many cases, a pratically 100% discrimination of one guest species (>95% by NMR integration) is achieved by a single crystallization process using *1*, e.g. from an equimolar two-component solvent mixture. Table 2 summarizes important results (Entries 1–15).

Selection at inclusion formation (see relative guest excess) is derived from steric as well as from chemical points of view. Hence, high discrimination is found for a combination of potential solvents differing in the functional group characteristic, e.g. if belonging to different classes of substances (see Entries 8–10). But also within the same class of substance, so far as a series of homologues and different substituted or branched compounds are concerned, discrimination is effected in up to a 90% ratio [33].

Table 2. Preference of guest binding of host *1* from a two-component solvent system

Entry	Recrystalln Solvent compd mixture (equimol ratio)	Relative guest excess, % g.e.
1	methanol/*ethanol*[a]	46[b]
2	methanol/*t-butanol*	91
3	*methanol*/toluene	14
4	*ethanol*/2-propanol	79
5	*ethanol*/t-butanol	92
6	ethanol/*benzyl alcohol*	20
7	ethanol/*ethylene glycol*	>95
8	*ethanol*/acetic acid	>95
9	ethanol/*dimethylformamide*	>95
10	*ethanol*/acetonitrile	>95
11	1-propanol/*2-propanol*	29
12	1-butanol/*t-butanol*	74
13	isobutanol/*t-butanol*	78
14	acetonitrile/*dimethyl sulfoxide*	>95
15	*acetonitrile*/toluene	42

[a] Solvents printed in italics refer to those preferentially enclathrated. [b] Determined by NMR integration of the isolated crystals after a drying period of 12 h at 0.5 torr.

For instance, the crystallization of *1* from an equimolar mixture of methanol/ethanol gave a distinct discrimination of methanol and yielded the corresponding ethanol inclusion compound in a relative guest excess (g.e.) of 46% (Entry 1). The discrimination coming from a 1:1 mixture of methanol/t-butanol was found to favor clearly t-butanol (g.e. 91%, Entry 2). This finding again shows the preferred binding of the higher homologues of methanol by the host lattice. However, in the case of the solvent mixtures ethanol/2-propanol and ethanol/t-butanol, the lower homologue, that is ethanol, is the preferred inclusion component (Entries 4 and 5).

A remarkable occurrence with the high preference for ethanol (g.e. 95%) takes place with the solvent pair ethanol/acetic acid (Entry 8) since the removal of acetic acid from any polar media is observed to be difficult. Preference for ethanol (g.e. >95%) is also observed in the presence of acetonitrile (Entry 10), but not in the presence of dimethylformamide (Entry 9). Here the ratio is reversed (>95% g.e. of dimethylformamide). In respective mixtures with ethylene glycol or benzyl alcohol, ethanol is not the favored guest component either (Entry 6 and 7). The high preference for ethylene glycol with respect to ethanol may proceed from a more extensive H-bonding pattern in the inclusion lattice in case of the glycol because of its bivalency. Benzyl alcohol, in the main, seems structurally well adapted to the aromatic moieties of the host molecule. The results of Entries 11–13 are emphasized by the fact that the higher branched analogues of propanol and butanol are favored for inclusion into *1*.

The practically complete discrimination of acetonitrile in favor of dimethyl sulfoxide (Entry 14) is also remarkable since both solvents are of the same category (dipolar aprotic) and, in addition, they have comparable polarities [34]. These facts are retained even when acetonitrile is of tenfold excess in a respective mixture with dimethyl

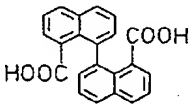
sulfoxide. In comparision, the preferred uptake of acetonitrile in a mixture with toluene (Entry 15) is a relatively trivial differentiation of molecules.

Selectivity at formation of a respective inclusion compound and its thermal stability behavior might differ (cf. Tables 1 and 2), since for both representations different processes should be taken into consideration. Formation of a crystal inclusion compound is normally controlled by kinetics, whereas the thermal stability (decomposition property) is a result of thermodynamics. Thus, we speak of "formation selectivity", on the one hand, and of "binding selectivity", on the other.

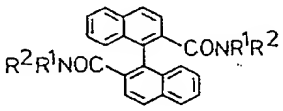
3.3 Scissor-like Host Molecules Having Altered Building Blocks

3.3.1 Examples of Selected Compounds

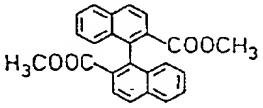
To probe the range of application of the new inclusion strategy (coordination-assisted clathrate formation) in different ways, directed structural modifications were undertaken starting from the basic constitution *1*, for instance as to the molecular skeleton (basic structure) and/or the sensor section (functional groups). The formulae *7–24* show different possibilities of such variations.



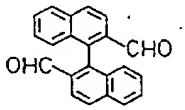
7



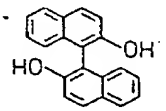
9 R^1 =H, R^2=H
10 R^1 =H, R^2=CH_3
11 R^1 =CH_3, R^2=CH_3



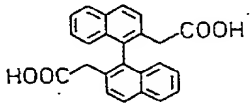
8



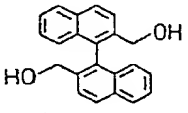
12



13

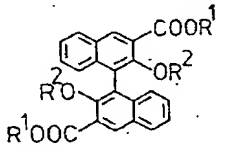


14

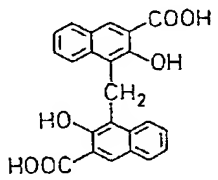


15

The fundamental components (basic skeleton and functional groups), of which *7* [35] is made up, are the same as in *1*, however, they are linked in a different way (8,8′- instead of 2,2′-position). On the other hand, compounds *8–13* (*8* [1], *9* [36], *10–12* [37], *13* [38]) have a skeleton identical to *1* and the same positioning of substituents, but contain functional groups differing from *1*, e.g. $COOCH_3$, $CONH_2$, $CONHCH_3$, $CON(CH_3)_2$, CHO, OH, respectively. At *14* [37] and *15* [1] (cf. *1* and *13*, respectively), modification is associated with a relation of homology (insertion of one CH_2 unit, each, between skeleton and functional group).

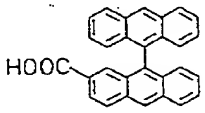


16 R^1 =H, R^2=H
17 R^1 =H, R^2=CH_3
18 R^1 =CH_3, R^2=CH_3

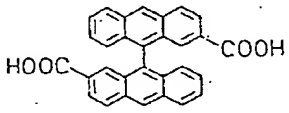


19

Enlargement to four functional groups in all (two hydroxyl and two carboxyl groups) is characteristic of *16* [39]; *17* [37,40] and *18* [37,40] are examples of comparison. Compound *19* [41] has an additional CH_2-group inserted into the rotation axis of the molecular hinge compared with *16*. Strictly speaking, this is no longer a molecule shaped like a pair of scissors. Enlargements including the basic skeleton, but without touching the scissor-like structure, are displayed in the bianthrylcarboxylic acids *20* [37] and *21* [42].

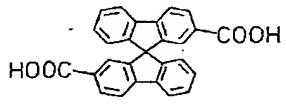


20

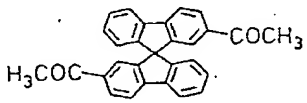


21

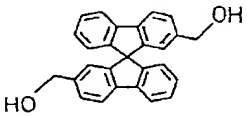
A completely different access to molecules with a scissor-like shape is opened up via spiro-linkage. Typical examples following this building principle are the spirobifluorenes *22* [43] and *23* [43] which differ also in the functional groups. In case of the spirocompounds, the flexible hinge is not applicable and the edges of the molecular scissors are fixed at an angle of 90°.



22



23



24

3.3.2 Inclusion Properties

Because of the superior inclusion properties exhibited by *1* [2], one may infer that the positional isomer with reference to the carboxylic group, *7*, also behaves as a good inclusion host. However, this is not true. So far, we have not succeeded in isolating any inclusion compound of an uncharged molecule using *7*, except those of a salt-like nature (see Sect. 4.2.2.). Obviously the functional groups of *7* are located in the molecule in a way that works against the net bulkiness of the skeleton (connected with the crystal build-up); in *1* they cooperate.

1,1′-Binaphthyls incorporating functional groups other than carboxyl (e.g. carbonamide, *N*-methylcarbonamide, formyl, hydroxyl, but not methoxycarbonyl and *N*,*N*-dimethylcarbonamide), however in the privileged 2,2′-position, again show crystal inclusion properties (Table 3) [37]. For instance, the biscarbonamide *9* forms stable inclusion compounds with dimethylformamide, acetic acid, propionic acid, and dioxane. By contrast, the *N*,*N*-dimethyl-substituted analogue *10* yields only an inclusion with acetic acid which is probably a result of the reduced H-bond

Table 3. Clathrate inclusion compounds of scissor-like hosts other than *1*

Host no	Guest compound	Host : guest mol ratio[a]	Host no	Guest compound	Host : guest mol ratio[a]
9:	acetic acid	1:1	*10*:	acetic acid	1:1
	propionic acid	1:1			
	dimethylformamide	1:1	*12*:	nitromethane	2:1
	dioxane	1:1		pyridine	2:1
				dioxane	2:1
13:	methanol	1:2			
	cyclopentanol	1:2	*16*:	dimethylformamide	1:2
	ethylene glycol	2:3		1-propanol,	[b]
	lactic acid	1:2		t-butanol	
	cyclopentylamine	1:1		dimethyl sulfoxide	[b]
	diisopropylamine	1:1	*17*:	bromobenzene	2:1
	di-t-butylamine	2:3		toluene	2:1
	dicyclohexylamine	1:1		acetone	[b]
	2,5-diamino-2,5-dimethylhexane	1:1		dimethyl sulfoxide	[b]
	4-chlorobenzylamine	1:1			
	4-hydroxybenzylamine	1:1	*19*:	dimethylformamide	1:2
	3-methylaniline	1:1			
	3,5-dimethylaniline	1:1	*20*:	dimethyl sulfoxide	1:1
	2,6-dimethylaniline	1:1			
	3-hydroxyaniline	1:2	*22*:	ethanol	2:1
	2-amino-6-methylpyridine	1:1		2-propanol	1:1
	imidazole	1:2		dimethylformamide	1:2
	piperidine	1:1		dioxane	1:1
	dimethylformamide	2:3		benzene	1:1
	dimethyl sulfoxide	1:2			
	acetone	1:1	*23*:	tetrahydrofuran	2:1
	acetylacetone	1:2		benzene	1:1
	dioxane	2:3		1-bromopentane	2:3
	tetrahydrofuran	2:3			

[a] Determined by NMR integration as specified in Table 1. [b] No clear stoichiometry.

mediatorship and *11*, lacking any mobile H, is completely ineffective. For the dialdehyde *12* mainly H-acceptor properties were assumed, hence protic guest molecules should be favored. Surprisingly, up to now, no crystal inclusions of *12* either with alcohols or with acids as guest molecules have been found, but only those with dipolar-aprotic solvents (Table 3). This behavior indicates, that the formyl substituent is a rather poor sensor group, e.g. in respect to hydrogen bonding.

Compound *13*, having two phenolic hydroxyls as potential sites instead, is rather different in its behavior [37]. No doubt, this compound is inferior to *1* in the variety of forming crystal inclusions as far as alcohols and acids as guests are concerned. However, it is an advantage that different amines (primary, secondary) or pyridines are included in the lattice to form inclusion compounds other than being derived from simple salt formation. Amines are even the favored inclusion partners of *13* as shown by the number and stability of the isolated inclusion compounds (Table 3). A prospective interpretation of this exceptional position is hydrogen bonding which seems particularly effective in the present host-guest combination. Recently Toda and Goldberg [44] reported the successful (chiroselective) inclusion of sulfoxides and phosphine oxides into the host lattice of *13* (see Chapter 3 in volume 140 of this series and Chapter 1 of this book).

Considering the competitive experiments, e.g. from two-component solvent mixtures (see Table 4), it is not surprising that the amines are always favored on inclusion formation (Entries 1—5). A remarkable point is also the ability of *13*, properly speaking its crystal lattice, to accommodate relatively voluminous guest molecules, among them many ring compounds (Tables 3 and 4). Hence, *1* and *13* are complementary in their inclusion behavior to some extent.

Hoping to achieve selectivity with regard to spatially more demanding guest species as in the case of *1*, the acetic acid-analogous compound *14* has been synthesized. Evidently the additional methylene units neighboring the functional groups, however, allow *14* too much conformational flexibility. Accordingly no lattice inclusion properties are observed from our tests [37]. The same holds for *15* (an analogue of *13* extended by a methylene group at each substituent).

From the beginning, compound *16* was expected to show only moderate "coordinatoclathrate behavior" since it should have a propensity for *intra*molecular H-

Table 4. Selective guest inclusion of host compound *13*

Entry	Recrystalln solvent compd mixture (I/II)[a]	Host:I:II mol ratio[b]
1	dimethylamine/acetone	1:1:0
2	diisopropylamine/acetylacetone	1:1:0
3	dicyclohexylamine/methanol	1:1:0
4	dicyclohexylamine/cyclopentanol	1:1:0
5	dicyclohexylamine/diphenylamine	1:1:0
6	morpholine/dioxane	1:x:y[c]
7	acetone/acetylacetone	1:x:y

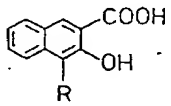
[a] Equimolar ratio. [b] Determined by NMR integration as specified in Table 1.
[c] No clear discrimination in favor of I or II.

bonding rather than *inter*molecular H-bridge formation with guest molecules as binding partners regarding the salicylic acid subunits. The experimental finding [37] confirms this presumption. The only inclusion compound having a defined stoichiometry which has been isolated is the 1:2 crystal inclusion with dimethylformamide (Table 3); besides 1-propanol, t-butanol, and dimethyl sulfoxide are accommodated with no clear stoichiometry.

The methoxy analogous compound *17* is not expected to have the same high potential of forming intramolecular hydrogen bonds opposing a possible host-guest binding. Nevertheless, we succeeded in the isolation of crystal inclusion compounds with typical aprotic (dipolar and apolar) guest molecules like dimethyl sulfoxide, acetone, bromobenzene [45], and toluene (Table 3). Moreover, the respective inclusion stoichiometries cause some difficulties in reproduction. The most unexpected result however is that *17* does not form a crystal inclusion with dimethylformamide; the tetramethyl compound *18* gave no crystal inclusion at all [37].

On the other hand, since the angular derivative *19*, whose constitution is characterized by two quasi-isolated hydroxynaphthalenecarboxylic acid subunits and whose structural analogy to a pair of scissors is removed for the most part, also yields an inclusion compound with dimethylformamide with strict stoichiometry of 1:2 [37], and only and exclusively this one (Table 3), it is obvious that the free salicylic acid unit might be the decisive factor for the preferred binding of dimethylformamide of this class of compounds.

The unequivocal proof is furnished by the crystal inclusion behavior of simple 2-hydroxy-3-naphthalenecarboxylic acid *25a* [46], and its 1-chloro derivative *25b* [37], since both allow the formation of a crystalline adduct ("clathratocomplex" [19]) with dimethylformamide with the expected 1:1 stoichiometric ratio [37]. Thus, the salicylic acid function (2-hydroxycarboxylic acid group) is shown to be an excellent sensor, or a good complementary site for the dimethylformamide molecule in solid state inclusion.



25a R=H
25b R=Cl

In case of the bianthrylmonocarboxylic acid *20*, one may predict the formation of a lattice inclusion at least with dimethylformamide, but we did not succeed in obtaining it [37]. Instead a stable 1:1 stoichiometric inclusion compound of *20* is readily obtainable (Table 3). The bianthryldicarboxylic acid *21*, which is a direct analogue of *1*, is not available in sufficient quantity to be tested in respect to its lattice inclusion properties.

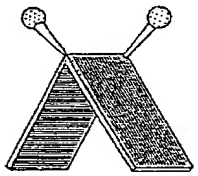
Changing of the flexible scissor-like element, as in *1*, to an orthogonal and rigid version of this element, as in *22*, reduces the activity of inclusion formation to a certain degree. Nevertheless very different guest molecules are readily accommodated in the crystal lattice of *22*, they are proton donors (ethanol, 2-propanol) [47], H-bridge acceptors (dimethylformamide, dioxane), or benzene as an unpolar solvent [48]

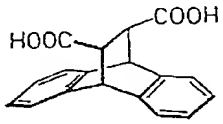
(Table 3). The crystal inclusion compounds of the protic solvents are distinguished by relatively high points of thermal decomposition and, as before, the inclusion compound with dimethylformamide exhibits the highest tendency of formation. This is the result of competitive experiments.

According to the coordinatoclathrate predict, the spiro compound *23* will not allow the formation of inclusion compounds with dimethylformamide and other polar solvents, but with benzene, tetrahydrofuran, and 1-bromopentane (Table 3). Due to the limited number of guest inclusions, a lattice cavity of rather restricted dimensions is suggested for *23*; e.g. toluene, cyclohexane or dioxane are not suitable guest partners for *23*, whereas lower homologues (cf. benzene, tetrahydrofuran) are readily included [37]. The behavior of a reduced analogue of *23*, the hydroxymethyl — substituted spiro compound *24*, is in some way comparable since an inclusion compound with benzene is the only one known; interestingly it is formed exclusively with optically resolved but not with racemic *24* [49].

3.4 Host Molecules Related to a Roof

There is no need for much fantasy to see the relation between a roof-shaped (Fig. 12) and a scissor-like basic structure (cf. Fig. 11). Nevertheless, the following point should be noted: Scissor-like molecules (cf. *1*) provide considerable (inherent) bulkiness merely due to the basic skeleton. On the other hand, as far as roof-shaped molecules are concerned [cf. *26* (Fig. 12) and *27–42*], the presence of polar substituents, suitably positioned, preferably at the top ridge of the molecular roof, are also instrumental in developing molecular bulkiness.

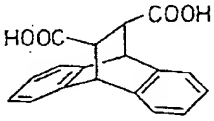




26

Fig. 12. Graphic design of a roof-shaped clathrate host (parent compound *26*)

Special features which characterize the prototypical roof-shaped compound *26* are a rigid molecular skeleton and the type of sensor groups used. They render *26* a potential coordinatoclathrand [50]. The capability of *26* in forming inclusion compounds is evident from Table 5. Here, nearly thirty different crystal inclusions of *26* are specified including as guest molecules various alcohols, acids, aprotic dipolar, and rather apolar species.



26

Considering this variety of crystalline inclusion compounds, *26* is close to *1* (cf. Table 1) and like *1*, the stoichiometries (host:guest) found for the different aggregates of *26* largely correspond to the expected ratios. Thermal stabilities in most cases are relatively high.

In contrast to *1*, however, inclusions of low-volume substrate species are hardly formed with regard to some of the series of compounds mentioned above. This is

Table 5. Clathrate inclusion compounds of roof-shaped hosts

Host no	Guest compound	Host:guest mol ratio[a]	Host no	Guest compound	Host:guest mol ratio[a]
26:	1-propanol	1:1	*35*:	dioxane	1:1
	1-butanol	1:1			
	t-butanol	1:1	*36*:	dioxane	2:1
	1-pentanol	1:1			
	1-octanol	2:1	*37*:	methanol	2:1
	ethylene glycol	1:2		t-butanol	1:1
	2-methoxyethanol	(1:1)[b]		ethylene glycol	1:1
	formic acid	1:2		epichlorohydrin	2:1
	acetic acid	1:1		diacetone alcohol	2:1
	propionic acid	1:1		dimethylformamide	3:2
	2-chloropropionic acid	1:1		dimethyl sulfoxide	1:1
	valeric acid	1:1			
	lactic acid	(1:1)[b]	*38*:	benzyl cyanide	1:2
	tartaric acid	2:1		dimethyl sulfoxide	1:2
	thioacetic acid	(2:1)[b]		dioxane	2:1
	mercaptoacetic acid	1:1			
	propionic aldehyde	1:1	*39*:	dimethylformamide	2:1
	acetone	1:1		dioxane	1:1
	dimethylformamide	1:1			
	acetonitrile	(1:1)[b]	*40*:	methanol	1:1
	benzyl cyanide	1:1		t-butanol	1:1
	dimethyl sulfoxide	1:1		cyclohexanol	1:1
	tetrahydrofuran	1:2		acetic acid	1:1
	dioxane	2:1		2-chloropropionic acid	1:1
	o-dichlorobenzene	1:1		lactic acid	1:1
	2,6-dimethylnitrobenzene	1:1		propionic aldehyde	2:1
	2-nitrophenol	1:2		acetone	2:1
				dimethylformamide	2:1
28:	ethylene glycol	1:1		dimethyl sulfoxide	1:1
	acetic acid	1:1		tetrahydrofuran	2:1
	propionic acid	2:3		dioxane	2:1
				morpholine	1:1
31:	methanol	1:1		piperidine	1:1
	formic acid	1:3		pyridine	2:1
	acetic acid	1:1		nitrobenzene	1:1
	propionic acid	1:1			
			41:	t-butanol	1:1
33:	tetrahydrofuran	2:1		dimethyl sulfoxide	1:2
	dioxane	2:1		dioxane	1:1

[a] Determined by NMR integration as specified in Table 1. [b] Unstoichiometric or low stability of the compound at atmospheric conditions.

quite clearly seen in the series of the unbranched alcohols: inclusion formation of *26* occurs neither with methanol nor with ethanol, but only beginning with 1-propanol to higher homologues up to and including 1-octanol (Table 5). Correspondingly, also for the carbonyl compounds and nitriles, the lower molecular mass representatives of these substance series are either not or only rather weakly accommodated into the host lattice of *26*. Referring to the carboxylic acids, however, differences in the size of molecules primarily influence the inclusion stoichiometries (e.g. formic acid 1:2, acetic acid and propionic acid 1:1, Table 5). This is perhaps a result of their high potency of forming H-bonded inter-substrate dimers.

The coordinatoclathrate relation appears from the examples as given in the following [50]: bivalent ethylene glycol forms a stable inclusion compound with *26*; gradual conversion into corresponding methyl ethers (2-methoxyethanol, monoglyme, respectively) leads to a loss of the inclusion formation (Table 5). On the other hand, the cyclic ethers tetrahydrofuran and dioxane allow isolation of thermally relatively stable crystal inclusions (range of decomposition 110–120 and 140–145 °C, respectively). This suggests that the functional groups of *26* are not completely available for guest binding, or can be used otherwise, e.g. for host-host interaction in order to stabilize an inclusion matrix. The stoichiometries (host:guest) differing in some cases from the expected ratios, e.g. 1:1 at the inclusion compound with dimethylformamide (half an equivalent of dimethylformamide per carboxylic group), but 1:2 in case of *1* (one dimethylformamide per carboxylic group), also point to the same fact.

Nevertheless, the inclusion of dimethylformamide in the lattice of *26* is found to be so much favored that this inclusion compound is pratically always obtained from competitive experiments [50] (Table 6), even in the presence of a larger excess of the second component. The results of other solvent combinations are less clear, showing that steric and electronic affects between host and guest superimpose in a way difficult to separate from one another. For instance, out of a mixture of acetic acid/1-butanol, the alcohol is selectively included by *26*, but from a mixture of acetic acid/1-octanol, it is the acid which is preferred; t-butanol/1-octanol yields the inclusion compound with 1-octanol. A mixture of 1-butanol/t-butanol leads to the formation of both kinds of inclusion compounds in about equal amounts. The t-butanol, however, is much more weakly bound in the lattice of *26* and thus evaporates completely from the crystal in a few days of storage in air, whereas the stoichiometric ratio of the respective 1-butanol inclusion compound remains unchanged for weeks. Hence 1-butanol compared with t-butanol is able to form the thermodynamically more stable inclusion compound with *26*, but from a kinetic point of view, inclusion formation with both butanol isomers is lacking in selectivity. Regarding a two-component solvent mixture of carboxylic acids, the spatially less demanding component is preferentially included by *26*, e.g. formic acid > acetic acid or propionic acid. But keep in mind, this fact contradicts the behavior of alcohols (Table 6).

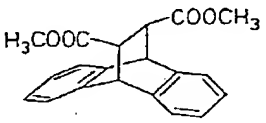
Probing the effect of functional group modification was achieved by using the compounds *27–34* [37,51] for the recrystallization experiments. These compounds are expected to show functional complementarity different to *26*. Table 5 summarizes the results. Inclusion compounds with protic and aprotic guest species are formed of *28*, *31*, and *33*, respectively. All the other potential hosts are ineffective. Hence it is demonstrated that the COPh groups of *33* are not suitable for coordinative

Table 6. Selective guest inclusion of some roof-shaped hosts from two-component solvent systems

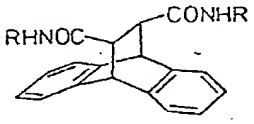
Host no	Recrystalln solvent compd mixture (I/II)[a]	Host:I:II mol ratio[b]	Host no	Recrystalln solvent compd mixture (I/II)[a]	Host:I:II mol ratio[b]
26:	1-propanol/1-butanol	1:0:1	*37*:	methanol/ethanol	2:1:0
	1-propanol/t-butanol	1:x:y[c]		1-butanol/t-butanol	2:0:1
	1-butanol/t-butanol	1:x:y		acetone/diacetone alcohol	2:0:1
	1-butanol/acetic acid	1:1:0			
	1-butanol/DMF	1:0:1			
	t-butanol/1-octanol	1:0:1	*40*:	methanol/ethanol	1:1:0
	t-butanol/ethylene glycol	1:0:1		methanol/cyclohexanol	1:0:1
	formic acid/acetic acid	1:1:0		cyclohexanol/ethanol	1:1:0
	formic acid/propionic acid	1:1:0		cyclohexanol/1-butanol	1:1:0
	formic acid/acetamide	1:1:0		cyclohexanol/t-butanol	1:0:1
	acetic acid/ethylene glycol	1:0:1		acetic acid/acetone	1:1:0
	acetic acid/1-octanol	1:1:0		propionic acid/acetone	1:0:1
	acetic acid/acetamide	1:1:0		propionic acid/propionic aldehyde	1:0:1
	acetic acid/2-chloropropionic acid	1:x:y		2-chloropropionic acid/propionic acid	1:1:0
	acetic acid/lactic acid	1:1:0		2-chloropropionic acid/lactic acid	1:1:0
	propionic acid/lactic acid	1:1:0		acetone/acetylacetone	1:1:0
	propionic acid/2-chloropropionic acid	1:x:y		acetone/acetonitrile	1:1:0
	DMF/piperidine	1:1:0		benzyl cyanide/nitrobenzene	1:0:1
	DMF/dioxane	1:1:0		4-cyanobenzaldehyde/4-chlorobenzylamine	1:0:1
	DMF/bromobenzene	1:1:0		morpholine/dioxane	1:1:0
	DMF/toluene	1:1:0		pyridine/benzene	1:1:0

[a] Equimolar ratio. [b] Determined by NMR integration as specified in Table 1. [c] No clear discrimination in favor of I or II.

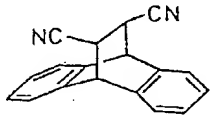
binding with protic guests, but use their bulk to form "true" clathrates with THF and dioxane. By way of contrast, the amide functions of *28* and *31* only combine with highly protic guests such as acids. Nevertheless steric effects apply also to the amide functional groups, since *29* and *30* which are the lower bulky analogues of *31* have unfavorable solubilities and failed in inclusion formation. On the other hand, the unsubstituted amide *28* may contribute four instead of only two hydrogens for guest binding and lattice build-up.



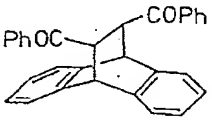
27



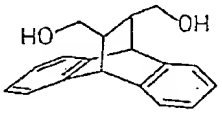
28 R=H
29 R=n-C_3H_7
30 R=i-C_3H_7
31 R=t-C_4H_9



32

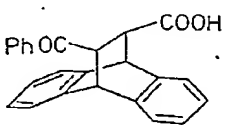


33

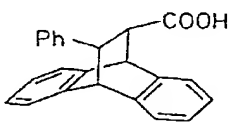


34

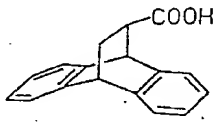
Retaining one of the COOH groups of *26* and modification or omission of the other one yields unsymmetric host compounds *35–37* [52], respectively. The interesting thing about it is that *35* and *36* behave much the same as *33*, i.e. formation of "true" clathrates with dioxane, whereas *37* forms inclusion compounds with guests typical of keeping up H-bonds to the carboxylic group [2,48]. Thus the inclusion behavior of carboxylic acids *35* and *36* is comparable to functional group free species (cf. Sect. 3.5) with no direct host-guest contact; *37* however is near to *26* with supposed strong host-guest interactions [37]. Considering an explanation of this remarkable behavior would necessarily lead into an analysis of the crystal packings and would require crystal structures (see Sect. 4.2).



35



36

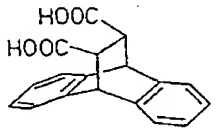


37

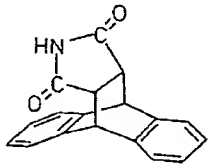
Another remarkable fact is that methanol acts as a suitable guest for *37* whereas long-chain alcohols are ineffective. The opposite is true for *26*. Since ethanol which is the next higher homologue of methanol does not lead to a corresponding crystal inclusion with *37* (the same applies for *31*), crystallization of *37* (or *31*) from respective solvent mixtures provides an easy way to separate methanol from ethanol,

or other higher alcohols [37]. The same holds for a solvent mixture 1-BuOH/t-BuOH since 1-BuOH is clearly discriminated against by *37*. Of pratical interest is also the clear discrimination against acetone in a mixture with diacetone alcohol (e.g. for the separation of aldol condensation products).

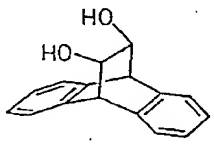
The next point in question refers to the effect of sterically different positioning of the functional groups at the roof-shaped skeleton. As is clearly shown from Table 5, the inclusion properties of the host compound *38* [53] having a *syn* instead of *anti* position of the carboxylic groups (cf. *26*) are restricted, especially in the uptake of hydroxylic guests (inclusion compounds are only formed with dimethyl sulfoxide, benzyl cyanide, and dioxane). This suggests that intramolecular H-bonding of the adjacent functional groups may have occured, neglecting the interaction with protonizable guests.



38



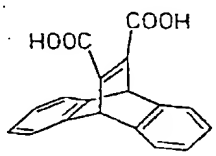
39



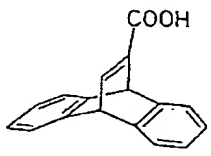
40

Modification of the carboxylic groups in *38* was effected by introducing functions as in *39* and *40* [54]. Both compounds proved to be inclusion hosts (Table 5). Although the two hosts are potential proton donors and acceptors, they show very different inclusion behavior [37]. The imide *39* forms inclusions with typical aprotic hosts (DMF, dioxane) and is thus in contrast with the amides *28* and *31* (see Table 5). The diol *40* provides broad inclusion properties which come near to *26*. Naturally there are some differences. The most striking one is that unbranched alcohols higher than methanol are not accommodated in the lattice of *40*. The stoichiometry ratios (host:guest) observed for the inclusion compounds of *40*, either 1:1 or 2:1 (Table 5), allow a possible distinction between protic and aprotic guest solvents, respectively. This may be interpreted as a result of the presence or the lack of coordinative binding participation as defined by the "coordinatoclathrate conception" (Sect. 2.2.).

The selective inclusion properties of *40* (Table 6) offer several possibilities of compound separation which are of interest in analytics and for preparation purposes [37]. The separation of methanol from a mixture with ethanol, or of propionic aldehyde from propionic acid, or of 2-chloropropionic acid from propionic acid or lactic acid, etc., are a few examples.



41



42

The unsaturated structures *41* and *42* [55] provide a third possibility of arranging functional sensor groups at the same roof-shaped skeleton in a given geometry. Here the sensors project in a perpendicular position with respect to the top ridge of the molecule instead of being inclined to one (cf. *37*, *38*) or both sides (cf. *26*) of the roof. In *41*, the carboxylic groups may interact intramolecularily, comparable to *38*. Consequently *41* and *38* display rather similar (and poor) inclusion properties [37] (Table 5), with one important difference however: unlike *38*, *41* allows the formation of an inclusion compound with t-butanol and, in addition, the stoichiometric ratios of the respective dioxane clathrates differ (1:1 in case of *41*, but 2:1 for *38*). In contrast to saturated monocarboxylic acid *37*, the unsaturated analogue *42* fails completely in inclusion formation [37].

3.5 Analogues Lacking Functional Groups and Related Compounds

Incorporation of coordinatively active complementary (functional) groups (in the host *and* the guest molecule) is an essential part of the "coordinatoclathrate idea" (see Sect. 2.2). In other words, in the absence of functional groups (Fig. 13), a so-called "coordinatoclathrate" is unimaginable. Also, under these circumstances coordinative linkage of the host molecules with each other to form a recticular matrix is not applicable (see. Sect. 2.1).

However, if Fig. 15a in Chapter 1 of Vol. 140 of this series ("Molecular Inclusion and Molecular Recognition — Clathrates I") applies, the absence of functional groups does not necessarily imply the failure of crystal inclusion formation, for instance when the molecular skeleton, as a result of inherent bulkiness (i.e. without coordinative binding assistance), provides favorable preconditions to form a clathrate (cf. Sect. 3.1). However, the selective binding character of a host owing to the so-called "sensor groups" (see Figs. 7 and 8) is of course lacking. In order to prove these assumptions, a series of accordingly modified compounds *43–55* have been synthesized. They display molecular skeletons related to the hosts described in the previous sections (3.2–3.4), but lack the typical functional groups of a coordinatoclathrate former.

The compounds *43* [56] and *44* [57] correspond to the compounds *1* and *7–18* (see Sects. 3.2 and 3.3), intended as coordinatoclathrate hosts, in the bulky binaphthyl hinge. Compound *44* provides methyl groups in a position (2,2') which was previously substituted by functional groups (cf. *1*), whereas *43* features the plain

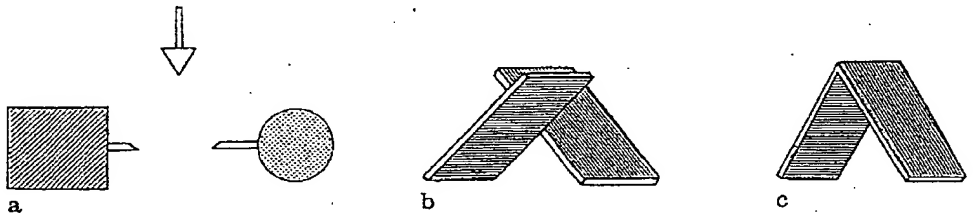
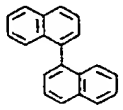
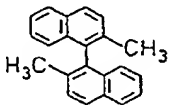


Fig. 13. Dismissal of functional groups (sensor groups) (a) effected at scissor-type and roof-shaped hosts (diagrammatic representation) (b and c)

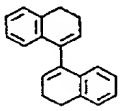
1,1'-binaphthyl base. The hydrocarbon *45* [58] possesses a partially hydrated binaphthyl skeleton which modifies the original geometry of scissors to some extent.



43



44



45

Considering the current knowledge (see above), one may assume that *43*, as well as *44* or *45*, are capable of forming crystal inclusions only with low-voluminous hydrocarbons using weak van der Waals forces. Contrary to all expectations, polar

Table 7. Clathrate inclusion compounds of functional group-free binaphthyl and bianthryl hosts

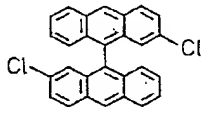
Host no	Guest compound	Host : guest mol ratio[a]	Host no	Guest compound[b]	Host : guest mol ratio[a]
43:	methanol	1 : 1	*47*:	2,3-dimethyl-2-butene (7.3)	1 : 1
	ethanol	1 : 1		cyclopentane (6.0)	2 : 1
	1-propanol	1 : 1		cyclohexane (7.0)	2 : 1
	1-butanol	2 : 1		cycloheptane (7.2)	[c]
	propionic acid	2 : 1		cyclooctane (7.8)	[d]
	acetonitrile	2 : 1		cyclopentene (6.0)	[d]
	3-aminopinane	1 : 1		cyclohexene (6.9)	2 : 1
	isoquinoline	1 : 1		cycloheptene (7.2)	[c]
	tetrahydrofuran	2 : 1		cyclooctene (7.7)	[c]
	dioxane	2 : 1		1,3-cyclohexadiene (6.9)	1 : 1
	cyclohexene	1 : 1		1,4-cyclohexadiene (6.9)	1 : 1
	2,3-dimethyl-2-butene	1 : 1		benzene (6.9)	1 : 1
	t-butyl chloride	2 : 1		cycloheptatriene (7.2)	1 : 1
				toluene (7.8)	[c]
				o-xylene (8.2)	1 : 1
				m-xylene (8.7)	1 : 1
				p-xylene (8.8)	1 : 1
44:	methanol	2 : 1		cyclopentanone (6.6)	[c]
	cyclohexane	(3 : 1)[c]		cyclohexanone (7.8)	1 : 1
				cyclohexene oxide (7.1)	1 : 1
46:	dioxane	(3 : 1)[c]		tetrahydrofuran (6.0)	1 : 1
	furan	(2 : 1)[c]		dioxane (6.8)	1 : 1
	pyridine	2 : 1		morpholine (6.8)	1 : 1
	cyclohexane	(3 : 1)[c]		piperidine (6.9)	1 : 1
	benzene	2 : 1		pyridine (6.9)	1 : 1
	toluene	2 : 1			
	m-xylene	(2 : 1)[c]			
	mesitylene	1 : 1			
	o-dichlorobenzene	2 : 1			

[a] Determined by NMR integration as specified in Table 1. [b] Numerical data in parentheses give the largest extension (Å) of guest molecules (based on van der Waals radii from space filling models, taking into consideration in most probable conformations, Ref. 65). [c] Unstoichiometric or low stability of the compound at atmospheric conditions. [d] Traces of solvent included.

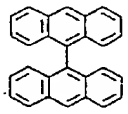
and even protic solvents are the guest species accommodated into the host lattice of *43* [37] (Table 7). So far, there is no reasonable explanation at hand for this particular behavior. However, recently indications appeared in outlines that weak intermolecular H bridges can exist between OH groups and aromatic π-systems (the OH group is assumed to be positioned perpendicular to a π-bond) [59]. One may also imagine a cluster formation of two or more guest molecules which mutually mask off their hydrophilic sites (cf. dimer formation of carboxylic acids in the clathrates of *26*; see Sect. 4.2.1), so as to be compatible with the apolar hydrocarbon-type host lattice. In favor of the latter assumption and against a possible polar interaction are the rather low thermal stabilities observed for these inclusion compounds. On the other hand, it is well known from the hydrate clathrates that molecules very different in chemical nature, e.g. water and a noble gas, are successfully assembled in a crystalline aggregate (cf. Sect. 2.1). But in these cases (and others) the apportionment of polarities on host and guest are reversed. Hence, the nature of the present crystal inclusions remains a critical point. Racemic binaphthyl *43*, in that respect, is polymorphous [60] and undergoes a solid-state transformation at moderate temperature rise (spontaneous separation into enantiomers) [61]. It is not too far from reality to assume that this background also plays a role for the unusual inclusion behavior of *43*.

The methyl-analogous compound *44* shows poor a tendency to crystallization which is possibly the reason why we succeeded in obtaining only a very limited number of inclusion compounds [37] (guest species methanol and cyclohexane; Table 7). The ability of a hydrocarbon host to combine with a polar guest molecule is retained, though. The hydrocarbon *45* with a partially saturated skeleton gave no respective inclusion compounds, although a "solvate" with acetic acid of the corresponding 7,7'-dimethyl derivative is reported [62].

Whereas the hydrocarbons with binaphthyl constitution *43* and *44* show rather unusual clathrate behavior, the crystal inclusion properties of the bianthryls *46* [42] and *47* [63] are in keeping with predictions made for potential hosts without polar groups. Accordingly, compounds *46* and *47* reject protic guests (like alcohols, carboxylic acids, etc.), without exception, but allow the formation of a great many crystal inclusions with *hydrocarbon* and a few with *dipolar-aprotic* guest molecules, among them ketones and heterocycles [64] (Table 7). The hydrocarbon host molecule *48* [43], for which the spiro compounds *22* and *23* are the underlying models, behaves accordingly [64] (Table 8).



46



47

A careful examination of the results given in Tables 7 and 8 reveal that with the exception of 2,3-dimethyl-2-butene (in the case of *47*) only *cyclic* guest molecules are taken up into the lattices of the host compounds *46–48*, but not the respective open-chain analogues. Saturated 2,3-dimethylbutane, as a compound for comparison, is not accommodated either, either by *46* or by *47*. Moreover, only cycles with distinct ring sizes (*five-* to *eight-membered* rings) are effective, indicating the presence

Table 8. Clathrate inclusion compounds of functional group-free spiro-type hosts

Host no	Guest compound	Host:guest mol ratio[a]	Host no	Guest compound	Host:guest mol ratio[a]
48:	cyclopentane	1:1	*49*:	benzene	3:2
	cyclohexane	1:1			
	cycloheptane	[b]			
	cyclopentene	1:1	*51*:	cyclohexane	3:1
	cyclohexene	1:1		benzene	1:1
	cycloheptene	2:1		tetrahydrofuran	2:1
	1,3-cyclohexadiene	1:1		dioxane	1:1
	1,4-cyclohexadiene	1:1		morpholine	1:1
	benzene	1:1		piperidine	2:1
	cycloheptatriene	1:1		pyridine	1:1
	p-xylene	2:1			
	cyclopentanone	1:1			
	cyclohexanone	1:1	*52*:	benzene	1:1
	cyclohexene oxide	1:1		pyridine	1:1
	tetrahydrofuran	1:1			
	dioxane	1:1			
	morpholine	1:1	*53*:	benzene	1:1
	piperidine	1:1		dioxane	1:1
	pyridine	1:1		pyridine	1:1

[a] Determined by NMR integration as specified in Table 1. [b] Traces of solvent included.

of crystal cavities with a defined geometry and similar dimensions (guest dimensions in Table 7). Referring to the alicyclic guests, cycloheptane and cyclopentane are the maximum and minimum molecular sizes, respectively, to be tolerated by *46* and *47*. Step-by-step introduction of double bonds into the larger ring homologues (e.g. as in cycloheptene, cycloheptatriene, or cyclooctene) causes a defined flattening of the rings. This obviously improves the spatial conditions and leads to the formation of crystal inclusions with *47* and *48* also in the range of seven- and eight-membered ring compounds (host:guest stoichiometries 2:1 or 1:1). Consequently it is also possible to distinguish in the field of cyclic guest compounds between *saturated* and *unsaturated* or *aromatic* molecules (e.g. cyclopentane from cyclopentene or toluene from methylcyclohexane).

Likewise it is possible to differentiate between *substituted* and *unsubstituted* alicycles using inclusion formation with *47* and *48*; only the unbranched hydrocarbons are accommodated into the crystal lattices of *47* and *48* (e.g. separation of cyclohexane from methylcyclohexane, or of cyclopentane from methylcyclopentane). This holds also for cycloalkenes (cf. cyclohexene/methylcyclohexene), but not for benzene and its derivatives. Yet, in the latter case no arbitrary number of substituents (methyl groups) and nor any position of the attached substituents at the aromatic nucleus is tolerated on inclusion formation with *46*, *47*, and *48*, dependent on the host molecule (Tables 7 and 8). This opens interesting separation procedures for analytical purposes, for instance the distinction between benzene and toluene or in the field of the isomeric xylenes.

Further important results of compound separation (two-component solvent mixtures) using hosts *47* and *48* are taken from Table 9 and are as follows [64]: *47* allows

Table 9. Selective guest inclusions of hosts *47* and *48* from two-component solvent systems

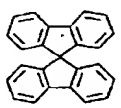
Host no	Recrystalln solvent compd mixture (I/II)[a]	Host:I:II mol ratio[b]	Host no	Recrystalln solvent compd mixture (I/II)[a]	Host:I:II mol ratio[b]
47:	toluene/benzene	1:x:y[c]	*48*:	benzene/toluene	1:1:0
	toluene/o-,m-xylene	1:x:y		benzene/o-,m-xylene	1:1:0
	toluene/pyridine	1:0:1		benzene/p-xylene	2:0:1
	toluene/dioxane	1:0:1		benzene/cyclohexane	1:x:y
	toluene/cyclohexane	1:0:1		benzene/cyclohexene	1:x:y
	cyclohexane/o-,m-,p-xylene	1:1:0		cyclohexane/cyclohexene	1:x:y
	cyclohexane/pyridine	1:1:0		cyclohexane/o-,m-xylene	1:1:0
	pyridine/tetrahydrofuran	1:1:0		cyclohexane/p-xylene	1:1:0
	pyridine/n-heptane	1:1:0		dioxane/THF	1:x:y
	pyridine/chloroform	1:1:0		dioxane/morpholine	1:x:y
	pyridine/dimethylformamide	1:1:0		morpholine/piperidine	1:x:y

[a] Equimolar ratio. [b] Determined by NMR integration as specified in Table 1. [c] No clear discrimination in favor of I or II.

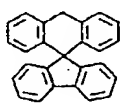
separation of cyclohexane from toluene, from xylene, and from pyridine, or of pyridine from toluene and from tetrahydrofuran, or of dioxane from toluene; *48* allows separation of cyclohexane from p-xylene, of p-xylene from benzene, etc. Differentiation between cyclohexane and benzene, or between cyclohexane and cyclohexene, however, is not complete with *47* and *48*.

The formation of crystal inclusion of *47* and *48* with cyclic ketones of suitable ring size (cyclopentanone, cyclohexanone) and with cyclohexene oxide are also important facts. Corresponding inclusion compounds with alcohols or amines could not be obtained. With reference to the heterocyclic guest molecules, the suitability of the ring size is likely to be the decisive factor for guest inclusion.

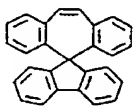
Comparison (Tables 7–9) shows that *47* and *48* are similar in their host properties, but they are not equivalent in behavior. Thus, host compound *48* is more qualified to select according to spatial aspects (see benzene derivatives) and, as a rule, it also forms the thermally more stable inclusions. This may be attributed to the rigid molecular geometry of the spirane *48*, whereas the biaryl *47* allows sterical adaptation to different guests via the flexible hinge to a certain degree.



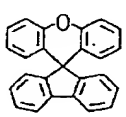
48



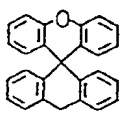
49



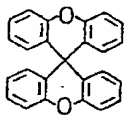
50



51



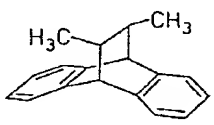
52



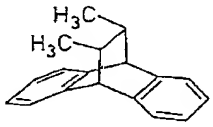
53

The series of spiranes *49–53* [37, 66], having a gradually altered constitution, demonstrate that in the range of the scissor-like molecules broad structural variabilities are possible. Compounds *49–53* differ in their molecular geometries from *48* in that the extra C and/or O atoms cause a more or less distinct bend at the "edges" of the molecular scissors. The general inclusion properties, however, are not fundamentally (except for *50* which gave no inclusions), but only gradually affected by this operation (Table 8), e.g. expressed in a reduced number of inclusion compounds [37, 64] compared to *48*. The inclusion stoichiometries are also different in some cases. Obviously, the mode of constitutional modifications as in *49–53* (restrictive of *50*) has only a secondary effect on the over-all lattice build-up and on the net geometry of the formed lattice voids.

The hydrocarbons *54* and *55* [51] which are functional group-free analogues of *26* and *38* display no activities of inclusion formation, either with polar or with apolar solvents [37]. This result is another proof that mostly for the roof-shaped type of compounds, functional groups play a fundamental role in the construction of a low-density packed crystal lattice.



54



55

Additional clathrate inclusions of this particular type of functional group free hosts have been studied by Toda and coworkers (see Chapter 3 in Vol. 140 of this series; "Molecular Inclusion and Molecular Recognition — Clathrates I").

The question arises about the crystal parameters which could be relevant for the clathrate properties and may reflect the observed inclusion selectivites.

4 Proving the Concept by X-Ray Crystallography

Crystal structure studies supply essential information about the solid state build-up of inclusion compounds, in principle. Due to the complexity of the problem, a full quantitative description of interactions between host and guest species in inclusion compounds can not be given by theoretical treatment as yet. Not only the most prominent primary interactions should be dealt with, but also effects due to the neighboring unit cells must be taken into account, since they also exert an influence on the entity to be considered. Such an *ab initio* approach has not been adopted until now. For this reason, the following discussion tends to describe some major effects in a somewhat qualitative manner. Because the argumentation relies on crystallographic data, directional parameters associated with the intra-aggregate attraction and repulsion of groups and segments are well to the fore. They involve H-bonding, van der Waals forces, and polarization.

At the beginning of these studies, the question was asked, whether such kinds of molecular associates may be really regarded as inclusion compounds, or as something

else which is sometimes called a "solvate". Now the associates considered here are well-defined inclusion compounds. Their solid-state structures demonstrate the particular way guest molecules are held in the crystal lattices. Another supporting argument is that many of the hosts described here provide a series of inclusions, whereas the use of the term "solvate" implies that they are individual cases. We are convinced that a study of the so called "solvates" in the structural literature may eventually lead to the discovery of other classes of inclusion compounds unknown as yet. For example, literature search in the Cambridge Crystallographic Database reveals 3471 entries named as organic "solvates" (state January 1986, Table 10.). It can be proven that many of these are in fact inclusions [67].

Accordingly, systematic studies offered by the designed host compounds are of importance precisely in the case of such classification problems. Therefore, the following discussion of the results of X-ray structure investigations is grouped to reveal that structural systematics exist for related host molecules ("coordinatoclathrate concept", see Sect. 2.2). This is best achieved by sorting inclusion compounds with the same *guest* molecules into one group. Classification of these solid associates will lead to the formulation of certain *recognition* principles for given guest molecules [67]. These may be understood as a characteristic pattern of their interaction with the host matrix in the crystal. Such an interaction pattern is mutually determined

Table 10. Output excerpt from a compound name search in the Cambridge Crystallographic Database showing independent occurrences of the search string "solvent" as a result of logical operations cross-referenced with different possible combinations of other denominations. (The final figure seems to be a pessimistic estimate)

INFORMATION FOR REFERENCES IN FILE 19 PRODUCED WHEN THE FOLLOWING TEMPORARY FILES WERE AVAILABLE			
1	255	WORD	CLATHRATE
2	2	WORD	INCLUSION
3	32	WORD	ADDUCT
4	563	WORD	COMPLEX
5	366	WORD	HYDRATE
6	541	WORD	AQUA
8	354	NOT	5 6
9	895	MERGE	6 8
10	881	NOT	9 1
13	876	NOT	10 4
14	3538	WORD	SOLVATE
15	3495	NOT	14 13
16	3487	NOT	15 1
17	3487	NOT	16 2
18	3484	NOT	17 3
19	*3471*	NOT	18 4

by accessible functional groups of both the host and guest molecules and of their respective shapes (*complementary* principle, see Fig. 8). Thus, alterations which do not grossly deformate structures of the individual host molecules will yield, somewhat trivially, to homology in their patterns of interactions with the same types of guest molecules in their crystals as well. Such systematics lay the basis of a kind of *supramolecular chemistry* which relies upon interactions between neutral associates of molecules.

4.1 Structures of Free Host Molecules

Usually the structures of inclusion compounds are more numerous. However, crystallographic studies involving free host molecules are no less important. At least they serve their purpose as a reference thus giving a broader basis for the understanding of the corresponding inclusions, too (cf. Refs. 12 and 16). Unfortunately, the study of free host structures is not always possible owing simply to the lack of proper single crystals. Such an unlucky case is compound *1*. Actually host compounds are intended to result in a loosely packed arrangement (cf. Sect. 3.1) and this means correspondingly an energetic instability of the would-be crystal. Hence we are caught on the horns of a dilemma. The outstanding inclusion ability of this host may be also due to the fact that a structure formed solely from the molecules of *1* is so unstable that virtually in all instances, inclusions are formed with quite a variety of solvents (cf. Table 1.).

In contrast to *1*, the related pure host *7* may be obtained in crystalline form [68]. The crystal structure of *7* is built *via* helical chains of alternating intra- and intermolecular H-bonding through the carboxyl functions. This structure supplies the information that the carboxyl groups are therefore already positioned in an appropriate way to facilitate analogous H-bonding in the known "inclusions" of *7*. As discussed later (Sect. 4.2.2), these are exclusively salt-type associates and as such, intimately interact with the carboxyl groups. Hence one may infer that displacement of the carboxyl functions from position 2 in *1* to position 8 in *7* reduces the ability of inclusion formation. Similar reasons such as the solid-solubility differences observed in the classical naphthalene/chloronaphthalene systems (alpha- *vs.* beta-substituted derivatives, cf. Ref. 28 may also be applied here.

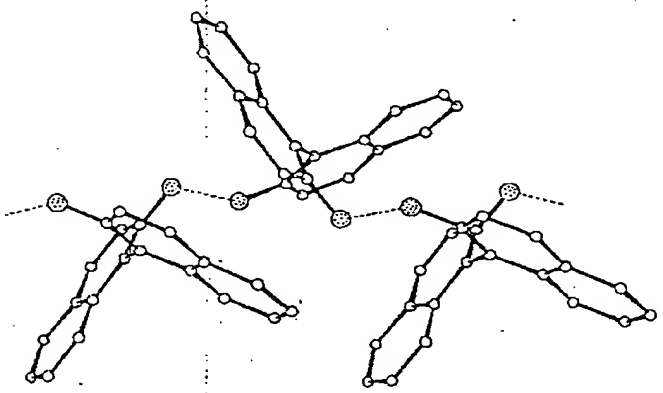


Fig. 14. H-bonding detail in the crystal structure of *13* (H-bonds as broken lines; O atoms dotted; H atom positions are not given in the reference) [69]

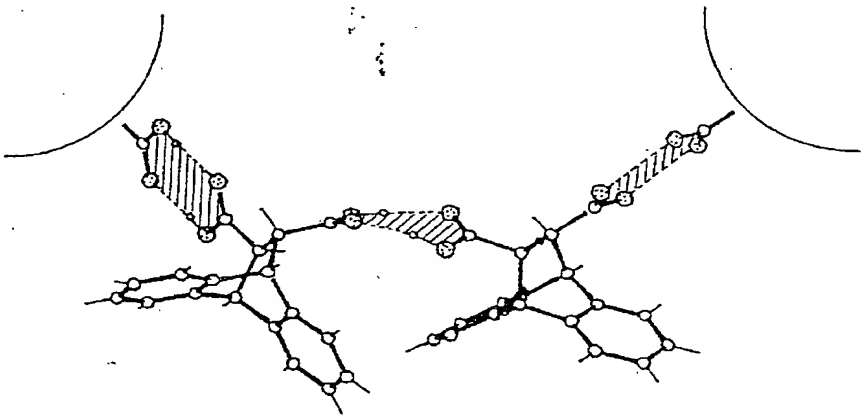


Fig. 15. Packing excerpt from the crystal structure of *26* [71] showing a central dimeric entity forming the asymmetric unit. The characteristic H-bond rings are indicated by hatching (H-bonds as broken lines; O atoms dotted; H atoms connected with non-heteroatoms are shown as sticks only)

The crystal structure of *13* was studied by Struchkov and his coworkers [69]. It is essentially characterized by its constituent molecules being placed in infinite H-bond helices (Fig. 14).

Compound *15* has an ill-defined structure [70] due to poor crystal quality. It is, however, interesting to note that *15* became resolved (space group $P2_12_12_1$, $Z = 8$) in an attempted cocrystallization experiment in the presence of optically pure *1*. The two molecules of *15* in the asymmetric unit may be seen as a sort of a "self inclusion", where molecules are again linked into infinite H-bond chains analogous to *13*.

The structure of *26* (Fig. 15) throws light upon the inclusion systematics of this roof-shaped host. A basic motif, apparent from the structure of the asymmetric unit

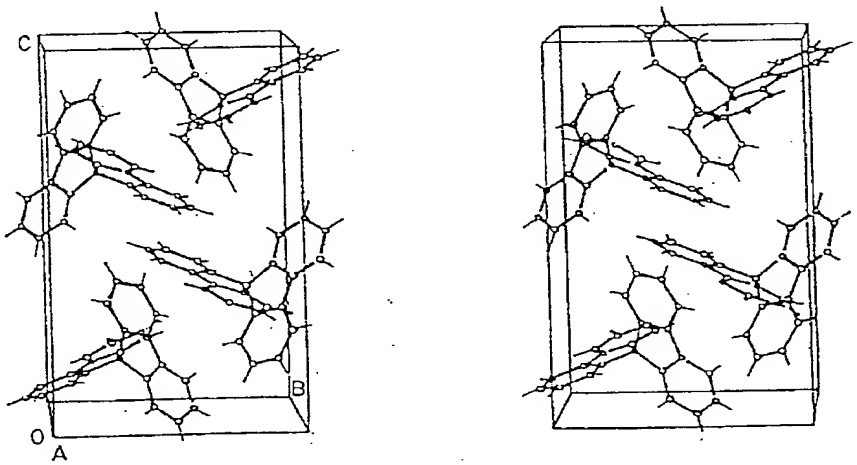


Fig. 16. Stereo drawing of the packing in the crystal structure of free host compound *48* [74] (H atoms are shown as sticks only)

of the pure host, is the formation of H-bonded dimers[71]. This pattern then returns in all known inclusions of *26* (see below), explaining the most common 1:1 stoichiometry. In spite of being a dicarboxylic acid, like *1*, *26* behaves (on inclusion) like a monocarboxylic acid with only one of its carboxylic groups free for binding to guest molecules, thus giving 1:1 host:guest ratios. The only exception where a 2:1 host:guest relation occurs is the aggregate of *26* with formic acid (Sect. 4.2.1). Nevertheless, this case neither contradicts the basic rule concerning the way of self-dimerization of the host *26* nor its consequences.

The structure of the parent compound *43* of the 1,1'-binaphthyl host family has been determined many times in independent laboratories and in different (racemic and resolved) crystal forms[60,61,72,73]. A common feature of both types of structure is that molecules of *43* form helices. Lateral contacts between such helices play an important role in the respective crystals. These spatial arrangements also emphasize the importance of the question concerning the presence of alpha or beta substituents' positioning as mentioned earlier[28].

Crystals of another pure hydrocarbon host *48* are formed in dimethyl sulfoxide[74]. Constituents of this structure are also arranged into helical arrays (Fig. 16).

4.2 Function of Sensor Groups in Binding Guest Molecules

Clathrate formation is determined by and large by an interplay of many different factors stemming from the shape and electronic properties of the host and guest assemblies. To some extent the role of the functional groups is transparent. They perform important control over the contact features by virtue of e.g. H-bonds to an eventual second (or even third) component of the aggregate. Their function parallels those of the recognition (sensoric) functions of higher organisms, hence the term "sensor group" seems appropriate. The great majority of the structures under discussion entails —COOH groups. In the following paragraphs, how this particular group (and in a few instances other groups as well) recognizes different classes of solvent guest molecules will be scrutinized.

4.2.1 Inclusion Compounds Involving Readily Deprotonizable (Proton-Donating) Guest Molecules: Alcohols and Acids as Guest Species

Alcohols as Guest Species

The high tendency of host *1* to form crystal inclusions was first demonstrated by its aggregates with alcohols[2]. At the same time, the nature of host-guest binding was also established by X-ray crystallography. The crystal lattices of these inclusions of *1* show similarities in their lattice parameters and symmetries (Table 11). The structures of the inclusion compounds between *1* and MeOH, EtOH, 2-PrOH, 2-BuOH, t-BuOH, 1-PrOH and ethylene glycol also illustrate some relations as shown by some selected characteristic examples (Figs. 17 and 18). Close resemblance in the binding mode of the guest entities is to be seen here. The first thing we learn from these structures refers to the —COOH groups of host *1*, as they perform their task, as expected, by building H-bonds to their opposing functions in the guest (cf. Table 12). The systematics of H-bonding patterns found in these crystals is also remarkable.

Table 11. Crystal data and packing coefficients for the alcohol inclusions of *1*

Compound[a]	*1a*	*1b*	*1c*	*1d*	*1e*	*1f*	*1g*
Space group	$P2_1/n$	$C2/c$	$C2/c$	$P\bar{1}$	$P2_1/n$	$P2_1/n$	$P2_1/n$
Unit cell							
a(Å)	15.642	11.737	12.051	10.160	12.009	10.603	14.276
b (Å)	14.532	14.522	14.776	14.050	12.747	14.377	9.533
c (Å)	9.292	13.769	14.362	15.167	14.982	15.664	15.556
α (deg)	90	90	90	100.37	90	90	90
β (deg)	95.14	101.50	102.53	104.4	105.52	104.2	109.19
γ (deg)	90	90	90	94.8	90	90	90
V (Å^3)	2104	2300	2496	2044	2210	2315	1999
Z	4	4	4	2	4	4	4
C_k[b]	0.75	0.75	0.74	0.71	0.75	0.71	0.77
D_c (gcm^{-3})	1.283	1.254	1.230	1.210	1.252	1.195	1.343

[a] Designation: *1a* = *1* · MeOH (1:2), *1b* = *1* · EtOH (1:2), *1c* = *1* · 2-PrOH (1:2), *1d* = *1* · 1-PrOH (2:1), *1e* = *1* · 2-BuOH (1:1), *1f* = *1* · t-BuOH (1:1), *1g* = *1* · ethylene glycol (1:1). [b] Packing coefficients calculated from the volume increments in Ref. 106.

Table 12. H-bonding data in the alcohol inclusion of *1* (cf. Table 11, and Figs. 17 and 18). E.s.d's are given in parentheses for the parameters involving non-hydrogen atoms only. Mean values and r.m.s.d.'s for the three groups (see footnote)[a] are 2.61(4), 2.66(4), and 2.74(7) Å from 10, 20, and 10 data of the unmarked, starred, and double-starred entries, respectively, of this table and of the corresponding entries of Table 13

Compound[b]	D ... A (Å)	H ... A (Å)	D-H (Å)	D-H ... A (deg)
1a	2.633(4)	1.66	0.98	171
	2.588(4)	1.54	1.05	172
	2.788(4)*	1.83	1.05	150
	2.734(4)*	1.79	0.97	161
1b	2.62(1)	[c]		
	2.66(1)*	[c]		
1c	2.676(3)	[c]		
	2.694(3)*	1.73	1.01	158
1d	2.589(3)	1.61	0.99	169
	2.727(3)*	1.74	1.03	160
	2.626(3)**	1.75	0.88	173
	2.595(3)**	1.64	0.97	166
	2.618(3)**	1.66	0.97	169
1e	2.565(3)	1.51	1.06	171
	2.693(3)*	1.75	0.95	173
	2.640(3)**	1.55	1.13	161
1f	2.547(8)	[c]		
	2.677(8)*	1.59	1.10	169
	2.611(9)**	[c]		
1g	2.615(3)	1.65	1.00	161
	2.654(2)	1.74	0.92	176
	2.917(2)*	1.99	0.97	157
	2.739(2)*	1.81	0.93	176

[a] Parameters marked with * derive from an alcohol donor and an acid (C=O) acceptor. Parameters marked with ** derive from a carboxyl(-OH) donor and carboxyl (C=O) acceptor (intermolecular). Entries not marked represent inverted relations. [b] For compound designation see Table 11. [c] No hydrogen atomic positions were determined for these sites.

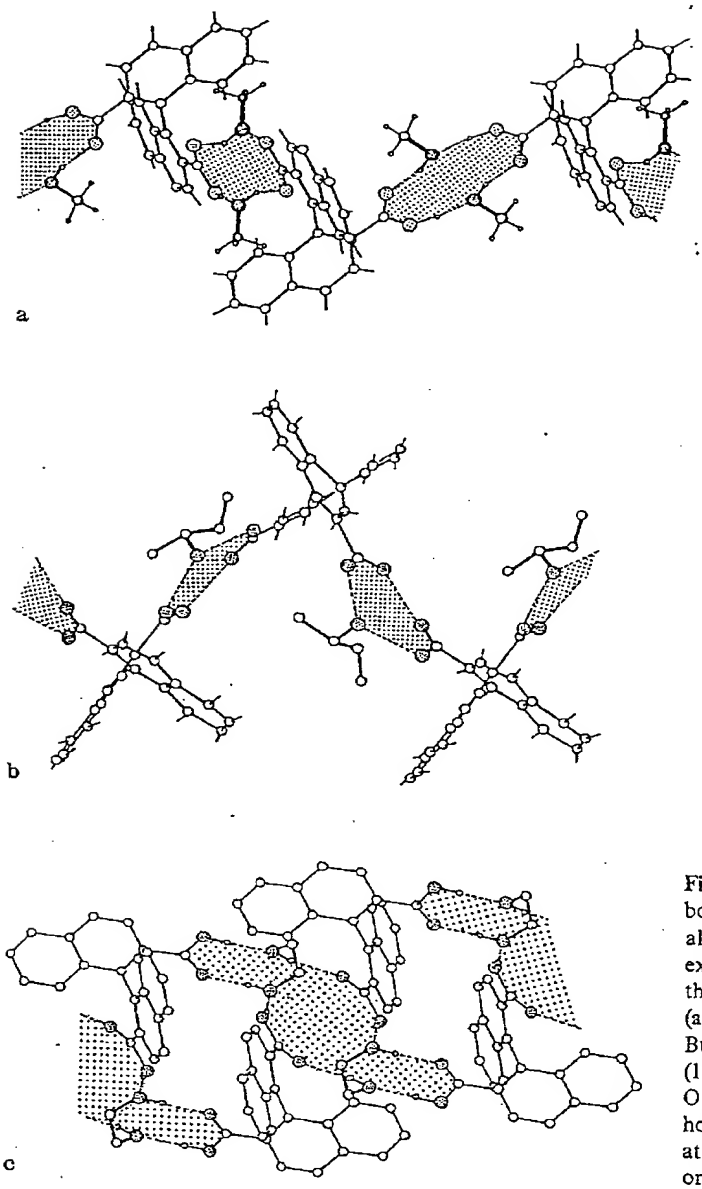


Fig. 17. Characteristic closed H-bond loops (shaded regions) in the alcohol inclusions of *1* [2]. Packing excerpts show the rings formed in the coordinatoclathrates (a) *1* · MeOH (1:2), (b) *1* · 2-BuOH (1:1), (c) *1* · ethylene glycol (1:1) (H-bonds as broken lines; O atoms dotted; H atoms of the host connected with non-hetero-atoms are shown as sticks only, or are omitted completely)

Hydrogen bonding is a phenomenon of considerable interest [75]. It is responsible for holding together many organic crystals. Also, H-bonding plays a major role in determining the conformations of nucleic acids, proteins and polysaccharides. Thus, H-bonds are involved in the formation of tertiary structures and in biomolecular recognition. Consequently, thorough understanding of their properties should assist us in modelling such complicated systems by artificial mimics of molecular association and recognition using simpler aggregates like the clathrates discussed here and the many other systems presented in different chapters of this volume. Unlike other kinds of weak interactions, H-bonding can be made more simply describable, in a similar

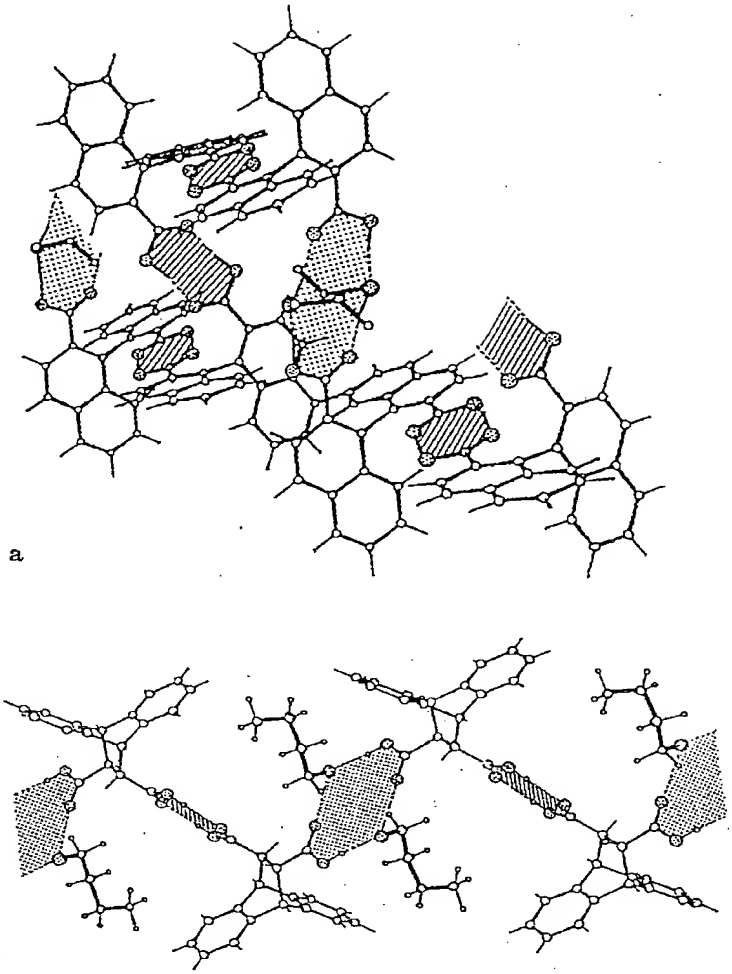


Fig. 18. Closed H-bond loops (dotted and hatched regions indicating host-guest and host-host interactions, respectively) in alcohol inclusions of *1* and *26*. Packing excerpts show the rings formed in the coordinatoclathrates: (a) *1* · 1-PrOH (2:1) [77], (b) *26* · 1-BuOH (1:1) [71] (H-atoms of the hosts are shown as sticks only)

way, as covalent bonds, i.e. in terms of distances and angles, which provides another advantage. Other kinds of interactions are less well describable and hence understood — they lack the accessibility of easy description typical of H-bonds. The interaction is not restricted to pairs of molecules within an asymmetric unit but, as revealed by the respective packing diagrams (abstracted in Figs. 17–19), involves a multitude of neighboring molecules.

The example specified as IIa in Fig. 19 reveals the pattern found invariably in the methanol, ethanol, and 2-propanol inclusions of *1*. It is characterized by a loop of H-bonds which always involves two guest molecules opposing each other through a center of symmetry and two carboxyl groups of two symmetry-related molecules of *1* thus having adverse chirality (Fig. 17a). The loop of H-bonds seems to be formed with

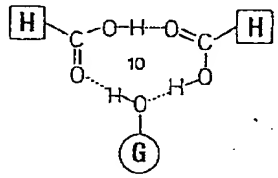
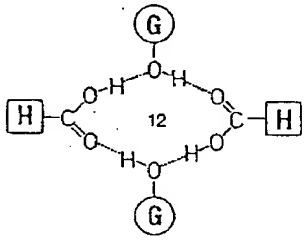
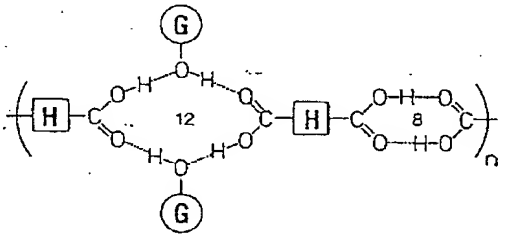
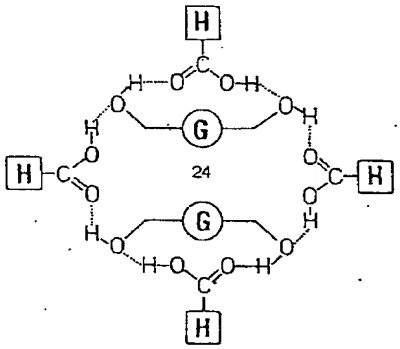
Type	Specification	Example
I		*1*·2-BuOH (1:1) (see Fig. 17b) *1*·t-BuOH (1:1)
IIa		*1*·MeOH (1:2) (see Fig. 17a) *1*·EtOH (1:2) *1*·2-PrOH (1:2)
IIb		*1*·1-PrOH (2:1) (see Fig. 18a) *26*·1-BuOH (1:1) (see Fig. 18b)
III		*1*·$HOCH_2CH_2OH$ (1:1) (see Fig. 17c)

Fig. 19. Systematics of the H-bond interactions found in the alcohol inclusions of *1* and *26* (the bold H stands for host, G for guest; A stands for acceptor, D for donor; the number in the center of the rings indicates the size, inclusive of H atoms)

directed donor-acceptor interactions corresponding to a homodromic arrangement [76]. This observation also applies to other clathrates of *1* with alcohols. Arrangements such as above are thought to possess slightly enhanced stability [76].

Examination of the steric relations in these complexes (cf. Fig. 30) suggests that the more voluminous branched alcohols cannot follow the same principle. Indeed, in the 2-butanol and also in the t-butanol inclusion compound, a different ring system is built (Fig. 17b and type I in Fig. 19). While the short-chain alcohols form twelve-membered H-bond loops, the branched butyl alcohols are embedded into a ten-membered asymmetric loop. The stoichiometry of the asymmetric unit also changes from 1:2 (host:guest) ratio to 1:1. The so-built ring system of homodromic H-bonds still contains a mirror-related pair of hosts *1*, but comprises only one guest molecule.

The ethylene glycol clathrate of *1* displays 1:1 stoichiometry, too. However, this guest has two —OH functions appended to a relatively small molecule. For that reason, it is able to form a rather huge (24-membered) centrosymmetric ring system (Fig. 17c and also type III in Fig. 19). It involves four carboxyl and hydroxyl groups, each coming from four host and two guest molecules, respectively. Yet, the building principle remains the same, involving host molecules of *1* of opposite chirality and H-bonds with homodromic direction.

A more deviating stoichiometry is found in the case of the inclusion compound of *1* with *1*-propanol [77]. Here the assistance of two independent host molecules is required and results in a 2:1 stoichiometry. Nevertheless, even this unusual host:guest ratio gives rise to a similar H-bond pattern (Fig. 18a and *type IIb* in Fig. 19) as found for the inclusions of *1* with simpler alcohols (cf. Fig. 17a), namely the 12-membered ring system. Now, another interesting fact arises, signalling the flexibility of host *1* in its inclusion behavior. This is the formation of host dimers through H-bonds to ensure clathration.

Precisely, this behavior is found for the host *26* (see Sect. 4.1), another properly tailored carboxylic acid (cf. Sect. 4.5). The crystal structure of the 1-butanol associate of *26* (Fig. 18b) shows the same 12-membered H-bond pattern around a center of symmetry as found for the inclusions of *1* with MeOH, EtOH, and 2-PrOH and exactly the same building principle (dimeric host and 12-ring formation) as in the 1-PrOH aggregate of *1*. Thus, they both belong to the same *type IIb* of building blocks (Fig. 19).

From these observations, we have noticed the similarity of the simple lattice inclusions to the more sophisticated assemblies of molecules (e.g. cyclodextrins [76] and proteins [78] where the formation of H-bonded loops was first detected and described. Conclusively the motive for the formation of simple inclusion crystals and of more complex associates between high and low molecular weight compounds, such as enzyme-substrate complexes, can be traced back to the same source.

The results clearly show the capacity of these hosts to act in coordinatoclathrate formation with hydroxylic group-containing guests which means a mutual coordinative relationship between the —COOH group of the host and of the —OH group of the guest is demonstrated. Another way of expressing the factual findings is to speak of mutual recognition between carboxylic hosts and hydroxylic guests originating from a particular association of the functional groups in the first place. Although the individual mode of the association shows some variation depending on the fine

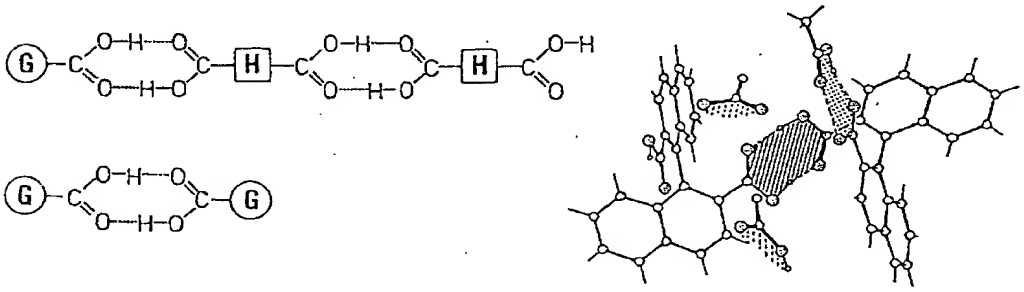
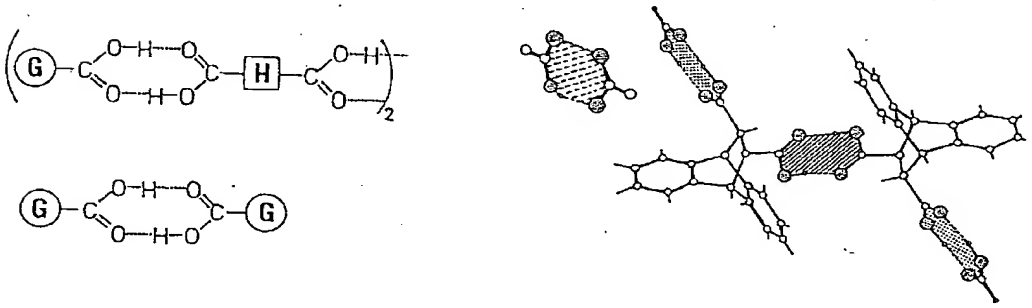
Type and specification	Example
I	 1 · H_3CCOOH (2:3)
II	 26 · HCOOH (1:2)
III	 26 · H_3COOH (1:1) 26 · H_3CCH_2COOH (1:1)

Fig. 20. Schematic and packing excerpt illustrations of the principal H-bond interactions found in the carboxylic acid clathrates of 1 [79] and 26 [50,71]. The bold H stands for host, G for guest. H-bond rings coming from either host-host, host-guest, or from guest-guest dimers are indicated by

tuning of the given host-guest combination, as e.g. expressed also in the number of the contributing partners, the principle of forming the associates is more general. It involves

- closed loops of homodromic H-bonds including —COOH and —OH;
- both enantiomers of the racemic acids are incorporated into this block (at least this applies for racemic alcohols);
- the full H-donor/acceptor capability of the attending groups is exploited.

A further general comment relates to the geometry of these H-bonds (Table 12) indicating strong interactions even when considering the reliability of H-atom positions. An interesting tendency is also seen in the mean values of the O ... O distances between different categories of H-donor/acceptor moieties (Table 12). The data seem to reflect the common difference in the chemical behavior of an alcoholic —OH (as a better H-acceptor) and of a carboxyl —OH (a stronger Brønsted-acid). For a verification, however, more accurate (H-atom position by e.g. neutron diffraction) and a larger number of data are required.

Acids as Guest Species

Inclusions of acids by *1* and *26* give rise to interesting findings. They surprise us by the constitution of their crystal lattices. For example, the inclusion of *1* with acetic acid has a 2:3 host:guest ratio [79] which is unusual for this host (see Table 1, Sect. 3.2.2). The constitution of the asymmetric unit reveals that the two molecules of *1* form a H-bonded dimer with each other (Fig. 20, type I), as also observed for the 1-PrOH inclusion of *1* (cf. Fig. 19, type II b) and those of the inclusions of *26* (see below). Such an entity binds one of the acetic acid molecules *via* mutual H-bond donor/acceptor relations forming a pseudo-dimeric arrangement. The two other independent guest molecules are arranged in tunnels in the crystal, made up by the first acetic acid complemented host matrix in the form of symmetry-center related H-bonded dimers.

A similar behavior is found in the 1:2 inclusion of *26* with formic acid [71] (Fig. 20, type II). We notice a H-bonded dimer of *26* and one of the formic acid molecules binding the host dimer in a pseudo-dimeric arrangement via the "free" —COOH groups of the host dimer. The second guest molecule is also placed into an interstitial tunnel of the dimeric host/bound-guest matrix. Here the 1:2 stoichiometry is due to the small size of the guest partner.

The structures of the acetic acid [50] and of the propionic acid [71] inclusions of *26* (Fig. 20, type III) are isomorphous to each other. The increased guest volume with respect to formic acid yields 1:1 stoichiometry, with no H-bonds between host and guest molecules in either case. The tunnel where the dimers of guests are situated (see Fig. 32a) is functionally the same as in the case of the self-dimerized pairs of the formic acid guests.

◀

different shading (hatched, dotted, and broken areas, respectively). Packing excerpt given for type III shows *26* · acetic acid (1:1). It stands for the isomorphous propionic acid clathrate als well (H-bonds as broken lines; O atoms dotted; H-atoms connected with non-heteroatoms are shown as sticks only)

All these known associates of *1* and *26* exemplify analogously structured crystals which may be regarded as either "true" clathrates (e.g. the acetic acid and propionic acid inclusions of *26*) or as "partial" coordinatoclathrates (acetic acid and formic acid inclusions of *1* and *26*, respectively). Depending on the spatial conditions and provided that the guest acids are small enough in size to fit into the intercoil clefts left free in the *1* and *26* host matrices, they intercalate and interact with the host —COOH at the same time. Obviously, acetic acid meets these criteria for *1* and formic acid for *26*. One may say that the size difference between the differing guest partners (formic acid *vs.* acetic acid) is well matched by the differences of the respective hosts *26* and *1*. The acetic acid and propionic acid guests are simply too voluminous to fit into a smaller cleft. Hence, they are placed into the more spacious tunnels formed by the *26* host matrix. This versatile manner of making inclusions of different strength has an obvious impact on the chemistry of these hosts, too.

The above class of inclusions shows unexpected features for one could well assume that guests will be coordinated strongly by the —COOH groups of host molecules (cf. alcohol inclusions). By way of contrast, in these examples all kinds of host-guest, host-host, and guest-guest H-bond contacts coexist, but exclusive host-guest contacts are never seen in these crystals. The geometry of the H-bonds may be assumed as being equally good for all types of these contacts (cf. Table 13). Hence, there is no obvious preference from these data alone as to which type of contact is the preferred one. Indications suggest that H-bonding is only a minor parameter in the mutual recognition of the carboxylic acid hosts and acidic guests. Actually the incidence of direct host-guest association is more a problem of spatial fit in the crystal than the presence of complementary functional groups, i.e. direct host-guest binding occurs

Table 13. H-bond dimensions in *26* (Fig. 15) and of its inclusion compounds with 1-BuOH (Fig. 18b) and acids (Fig. 20) as guest partners

Cmpd[a]	D—H ... A	D ... A (Å)	H ... A (Å)	D—H (Å)	D—H ... A (deg)
26	O18—H18 ... O14′	2.650(5)	1.69	0.98	167
	O15′—H15′ ... O17	2.759(5)	1.84	0.92	173
	O18′—H18′ ... O17′	2.705(5)	1.83	0.90	166
	O15—H15 ... O14	2.681(4)	[b]		
26a	O15—H15 ... O1b	2.599(5)	1.72	0.88	176
	O18—H18 ... O17	2.646(4)	1.83	0.82	173
	O1b—H1b ... O14	2.741(5)	[b]		
26b	O15—H15 ... O1f1	2.690(4)	1.62	1.07	174
	O18—H18 ... O17	2.647(3)	1.67	0.98	175
	O2f1—Hf1 ... O14	2.676(4)	1.74	0.94	172
	O2f2—Hf2 ... O1f2	2.640(5)	1.67	1.09	146
26c	O15—H15 ... O14	2.663	1.67	0.99	171
	O18—H18 ... O17	2.634	1.67	1.02	169
	O2a—H2a ... O1a	2.674	1.72	0.95	178
26d	O15—H15 ... O14	2.661(4)	1.76	0.93	163
	O18—H18 ... O17	2.651(4)	1.78	0.89	165
	O2a—H2a ... O1a	2.647(4)	1.59	1.08	167

[a] Designation: *26a* = *26* · n-BuOH (1:1), *26b* = *26* · formic acid (1:2), *26c* = 26 · acetic acid (1:1), *26d* = *26* · propionic acid (1:1). [b] These H atoms could not be located.

only when a small enough guest molecule is available and is being used for possible stabilization of the crystal. The pK-difference between acids may also add some drift towards such behavior.

4.2.2 Inclusion Compounds Involving Readily Protonizable (Proton Accepting) Guest Molecules: Salt-type Associates and Ternary Complexes of 7 and Imidazole Clathrate of 13

Salt-Type Associates and Ternary Complexes of 7

Though molecules *1* and *7* are closely connected in structure, they have totally different host properties, i.e. *1* readily forms inclusion compounds with a wide variety of guests (see Sect. 3.2.2) while *7* does not. For example, crystals of the pure host could be obtained from dimethylformamide, a solvent which is tightly held by *1*. Reasons for the different behavior of *1* and *7* have already been mentioned when the crystal structure of the free host *7* was discussed (Sect. 4.1). However, the ability of *7* to form a crystalline associate is increased, if a solvent with the property of a base is present, e.g. pyridine and substituted derivatives of pyridine (see Table 14) [80].

As confirmed by the structural studies, proton transfer from one of the carboxyl groups of *7* plays a principal role in these events (salt formation). Obviously this process is faciliated by the same factor as already seen in the structure of solvent-free *7*, namely the favorable steric placement of the two carboxyl groups. The principle of forming these salt-type inclusion aggregates is best demonstrated by the crystal structure given in Fig. 21 as type I which shows the structure of the 1:1 associate of *7* with pyridine. The same type I arrangement applies for the 1:1 associate of *7* with 2-(hydroxymethyl)pyridine. The carboxylate anion arising from the host molecule is stabilized by the internal (intramolecular) H-bond from the *syn*-positioned —OH of the neighboring carboxyl group in both cases. Besides, there is a direct contact between the charged species.

The ternary aggregate composed of *7*, pyridine, and acetic acid with 1:1:1 stoichiometry composition (Fig. 21, type II) is an even more interesting case. Apparently

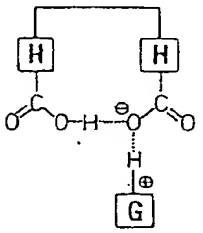
Table 14. Crystal data of the inclusion associates of *7*

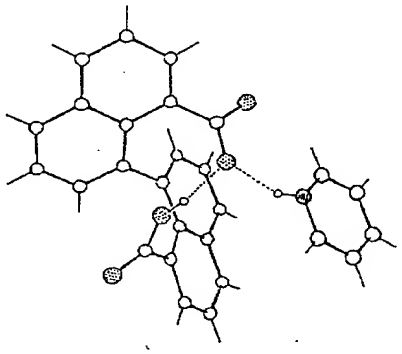
Compound[a]	*7a*	*7b*	*7c*	*7d*
Space group	$P2_1$	*Pbca*	$P\bar{1}$	*P*1
Unit cell				
a (Å)	8.080(1)	15.4267(4)	14.525(6)	7.569(4)
b (Å)	17.254(2)	21.1895(6)	10.481(4)	8.393(2)
c (Å)	7.715(1)	13.3727(4)	8.862(4)	8.634(1)
α (deg)	90	90	105.69(4)	93.21(2)
β (deg)	106.28(3)	90	111.10(6)	106.88(3)
γ (deg)	90	90	86.37(6)	105.17(3)
V (Å^3)	1032.4(3)	4371.3(2)	1211(1)	501.3(7)
Z	2	8	2	1
D_c (gcm^{-3})	1.356	1.372	1.321	1.359

[a] Designation: *7a* = *7* · pyridine (1:1), *7b* = *7* · 2-(hydroxymethyl)pyridine (1:1), *7c* = *7* · pyridine · acetic acid (1:1:1), *7d* = *7* · imidazole (1:1).

Type and specification	Example

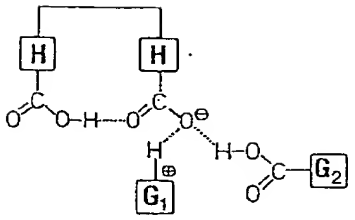
I





7 · Pyridine (1:1)

II



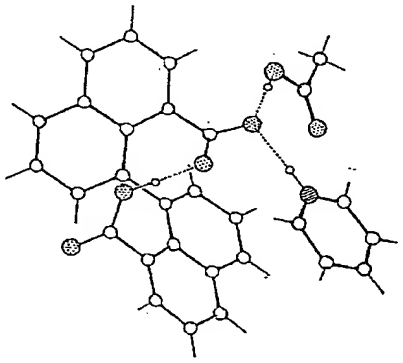


Fig. 21. Schematic and packing excerpt illustrations of the principal H-bond interactions found in the salt-type associates of 7 [80] (the bold H stands for host, G for guest; H-bonds as broken lines; O atoms dotted; N atoms hatched; H atoms connected with non-beteroatoms are shown as sticks only). The 7 · 2-(hydroxymethyl)pyridine (1 : 1) associate follows nearly the same principle as shown for type I

by virtue of the basic component (pyridine), the bimolecular salt-type associate 7 · pyridine (cf. Fig. 21, type I) became a host for a third partner (acetic acid). The intra-associate interactions may be characterized as before, involving strong H-bonds between the ionic species and internal contact of the carboxylic groups.

In summary, we may establish that the salt-type of inclusions and the ternary complex of 7 are determined by H-bonding in other respects. Here the characteristic property is the formation of strong intra-associate H-bonds (Table 15). Considering the invariable intramolecular involvement of one of the —COOH groups in the host,

Table 15. H-bond dimensions in the inclusion associates of *7* (cf. Fig. 21)

Cmpd[a]	D—H ... A	D ... A (Å)	H ... A (Å)	D—H (Å)	D—H ... A (deg)
7a	O(11)—H(11) ... O(11')	2.585(4)	0.88	1.73	163
	N(1P)—H(1N) ... O(11')	2.620(5)	0.96	1.68	166
7b	O(11)—H(11) ... O(11')	2.497(3)	0.99	1.52	172
	N(1P)—H(1N) ... O(11')	2.719(5)	0.97	1.76	171
	C(P2)—H(P2) ... O(10')[b]	3.068(5)	1.08	2.30	127
	O(P3)—H(30) ... O(10)[c]	2.739(5)	0.95	1.86	153
7c	O(11)—H(11) ... O(11')	2.576(3)	0.96	1.56	178
	N(P1)—H(N1) ... O(10')	2.692(4)	1.08	1.62	169
	O(A2)—H(A2) ... O(10')	2.623(4)	0.83	1.80	177

[a] For designation see Table 14. [b] Might be taken as a consequence of an already present H-bond. [c] Atom of a symmetry related molecule.

the major cohesion of the lattices is due to dispersion forces and van der Waals interactions. The only inter-associate H-bond exists in the structure of the *7* · 2-(hydroxymethyl)pyridine system involving —OH groups of symmetry-related solvent molecules. This associate also has a short C—H ... O contact [75b].

Apart from the isomeric relation between *7* and *1*, the appearence of the ternary associate now showing coordinatoclathrate properties gives a reasonable motive for putting up these compounds for discussion here. The dimer formation of carboxylic acids known from the related inclusions of *1* and *26* does not occur here. Instead, one observes a well-balanced system of H-bonds between groups of different acid/base properties. It is left to future studies to find other acid/base combinations which give a comparable situation. Actually, such H-bonded systems remind one of the multiple non-bonded interactions at the active centers of enzymes.

Imidazole Clathrate of the Non-Carboxylic Host 13

The binaphthol *13* is different from *1* and *7* owing to the lower acidity of its functional groups. Therefore, crystalline complexes of *13* with amines (see Table 3) are not expected to have a salt character. The *13* · imidazole 1:2 complex (Fig. 22) [81] was studied in the light of the general interest in this guest partner and its relation to alcohol functions in biological ensembles. The host molecule adopts ideal twofold

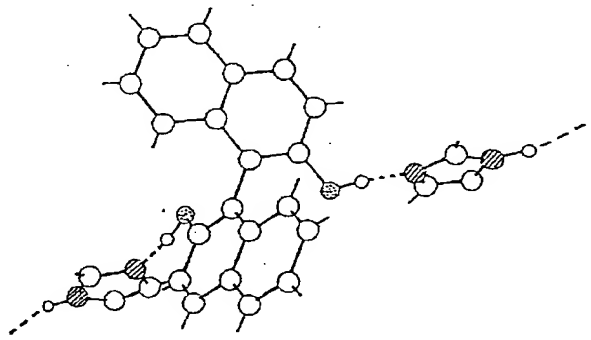


Fig. 22. H-bonding detail in the crystal structure of the *13* · imidazole (1:2) inclusion [81] (H-bonds as broken lines; O atoms dotted; N atoms hatched; H atoms connected with non-heteroatoms are shown as sticks only)

symmetry. The imidazole molecules are linked into an infinite spiral with host molecules as H-bond donor/acceptors complementing the role of the alcohol functions (Fig. 22). The tetragonal crystal lattice consists of hosts of the same chirality (i.e. spontaneous resolution occurred). Further examples of crystal structures of inclusion compounds of *13* including enantiodifferentiation phenomena are given in Chapter 1 of this volume (see also Chapter 3 of Vol. 140 of this series).

4.2.3 Inclusion Compounds Involving Aprotic-Dipolar Guest Molecules: Dimethylformamide and Dimethyl Sulfoxide as Guest Species

The guest compounds discussed under this heading have a somewhat reduced ability to establish H-bond interactions to the host matrix. They may well act as H-bond recipients using the negatively polarized part of their dipoles, but normally their H-donor capability is low. Corresponding behavior is observed in the crystalline inclusion compounds of *1*, *20*, *22*, *25b*, *26*, *37*, and *41* with dimethylformamide and dimethyl sulfoxide. On the one hand, their crystal structures (Figs. 23 and 24) indicate the way how the hosts recognize the different guest molecules. On the other hand, an analysis of the patterns of binding between different hosts and the same guest supplies us with information on the structural conditions for recognition of a given sensor group (the —COOH group in these host compounds).

Dimethylformamide (DMF) as Guest Species

In the first instance, it is important to notice that all inclusion compounds between dimethylformamide as guest and carboxylic acid hosts so far formally studied have the same 1 : 1 stoichiometry (each *free* —COOH of the host binds one dimethylformamide). The schemes of the characteristic binding modes including the structures are illustrated in Fig. 23. These arrangements prove the mutual H-bond donor/acceptor ability of the sensor groups both of the host (—COOH) and of the guest. In the latter, the donor function resides in the slightly acidic C—H of the formyl group.

Closer inspection of the blocks in the crystal structure, however, reveals some interesting variation as far as the individual spatial arrangements are concerned. The most compact association is found in the 1 : 2 inclusion compound of the spiro host *22* with dimethylformamide [48] (Fig. 23, type Ia). This aggregate preserves a perfect twofold (C_2) molecular symmetry in the crystal lattice. The formamide moiety acts as

---

▶

Fig. 23. Recognition characteristics of dimethylformamide emanating from the carboxylic host molecules studied [48,71,82,83]. Representative crystal structure excerpts and guest-binding schematics are shown parallel. The bold H stands for host, G for guest; A stands for acceptor, D for donor. H-bond rings coming from either host-guest or from host-host interactions (cf. type II) are indicated by different shading (dotted and hatched regions, respectively); single H-bonds are represented by a single broken line. Note that one of the DMF molecules in type Ib shows single binding only. Type Ic is characterized by an additional six-membered ring formed through an internal H-bond (O atoms dotted; N atoms hatched; H atoms connected with non-heteroatoms are shown as sticks only, except for the host molecules which are fully drawn)

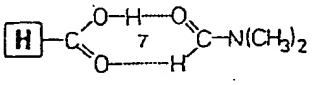
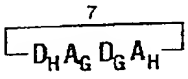
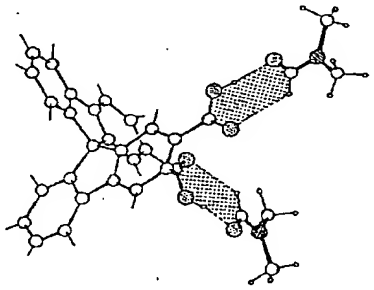
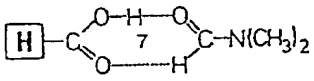
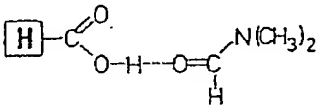
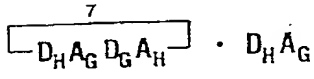
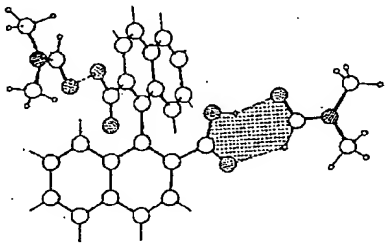
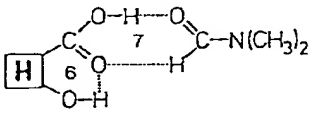
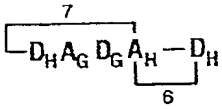
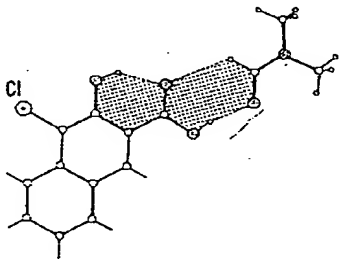
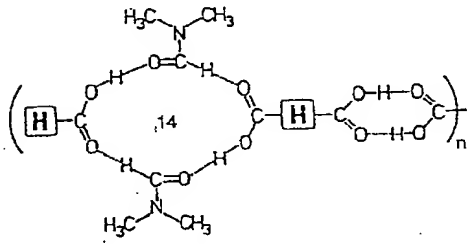
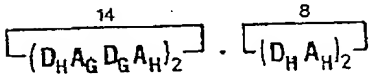
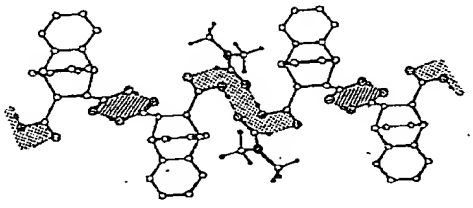
Type and specification	Example
Ia  	
Ib   	*22* · DMF (1:2)  *1* · DMF (1:2)
Ic  	 *25b* · DMF (1:1)
II  	 *26* · DMF (1:1)

Table 16. H-bond dimensions in the dimethylformamide inclusion of *1*, *22*, *25b*, and *26* (cf. Fig. 23)

Cmpd	D—H ... A	D ... A (Å)	H ... A (Å)	D—H (Å)	D—H ... A (deg)
1	O11—H11 ... O1d	2.692(6)	1.90	0.86	152
	O11'—H11' ... O1d'	2.613(6)	1.81	0.84	159
	C1d—H1d ... O10[a]	3.054(8)	2.26	1.08	129
22	O16—H16 ... O1d	2.593(2)	1.69	0.92	167
	C1d—H1d ... O15[a]	3.112(3)	2.42	0.99	126
25b	O11—H11 ... O1d	2.539(4)	1.74	0.82	167
	C1d—H1d ... O10[a]	3.255(3)	2.57	1.01	125
	O12—H12 ... O10	2.578(2)	1.82	0.87	144
26	O18—H18 ... O17	2.616(3)	1.76	0.87	170
	O15—H15 ... O1d	2.623(3)	1.74	0.89	179
	C2d—H2d ... O14[a]	3.240(4)	2.25	1.04	160

[a] Maintains a C—H ... O close contact.

H-bond acceptor from the carboxylic sensor of the host and also as donor making a C—H ... O type of interaction possible. In such a way, a 7-membered closed ring is formed, classified in the schematical representation as type Ia. This aggregate shows strong binding of the solvent molecule to the host as judged from the geometry parameters (Table 16).

The structure of the *1* · dymethylformamide 1:2 inclusion [82] is quite different from such a compact arrangement. One of the bound dimethylformamide molecules does not profit from keeping a cooperative C—H ... O interaction with its anchoring —COOH group here (Fig. 23, type Ib). This is due to probable packing conflicts caused by a similarly tight arrangement as in *22* (cf. Fig. 33, Sect. 4.4). One of the guest molecules is bound in a 7-membered, nearly co-planar arrangement (Tab. 16), while the other guest shows a linear binding to the anchoring carboxyl, still being co-planar with it.

Another example of dimethylformamide binding to a host is offered by the structure of the crystalline 1:1 associate with *25b* (Fig. 23, type Ic) [83]. This structure also shows the most frequent arrangement of the sensor function and the guest. The spatial correspondence between the carboxyl function and the amide moiety is also described by the dihedral angle (10.3 degrees) formed by these two moieties. The non-bound contacts (Table 16) indicate marginal (if any) interactions with the C—H moiety of the amide. This is most probably due to the presence of the —OH substituent at position 2 and the chlorine atom at position 4 in the "host" which exert substituent effects on the naphthalene moiety and give rise to an internal 6-membered H-bound ring maintained by the hydroxyl and carboxyl functions. As a result of this interaction, the carbonyl oxygen of the acid may become a weaker external acceptor.

An even more deviating pattern is found in the case of the *26* · dimethylformamide 1:1 clathrate [71] (Fig. 23, *type II*). Here, we see at first glance an arrangement that is similar to the situation found in the 1-BuOH inclusion of the same host (cf. Fig. 18b), or in the simpler alcohol inclusions of *1* (cf. Fig. 17a). A 14-membered ring is formed which formally corresponds to the sum of two 7-membered rings. The guest molecule acts as a H-bond acceptor with regard to the carboxyl group. Moreover, the formamide moiety still acts as a C—H ... O bond donor, in spite of the

fact that the guest moiety is visibly no longer coplanar to either of the —COOH functions. Clearly, the system is attempting to adapt to the environment as well as possible, partly dictated by the dimerically associated hosts. The *anti* positioned —OH bond of the coordinating carboxyl group is remarkable. This bond usually adopts that position when salt formation occurs, e.g. in the salt-type associates of *7* (cf. Fig. 21). Placement of the H-atom under discussion in the common *syn* position would result in steric conflicts with the H-atom of the formamide moiety. Possibly the system tries to escape from this unfavorable situation and thus finds an energetically advantageous solution to maintain coexistence of both the C—H ... O and the O—H ... O interaction by shifting the O—H bond into the less common *anti* position. This fact also signals the importance of the C—H ... O interaction.

Summing up, recognition of dimethylformamide may be given from the information obtained in the following statements:

— the oxygen atom of dimethylformamide is always a H-bond acceptor;
— advantage is taken of electrostatically favorable C—H ... O types of contacts whenever possible;
— dimethylformamide tends to approach a coplanar conformation with the anchoring —COOH group;
— by virtue of these principles, dimethylformamide has a preference for forming a 7-membered ring partly sustained by two H-bonds of O—H ... O and C—H ... O type between the counterfacing and more or less co-planar amide and carboxyl groups.

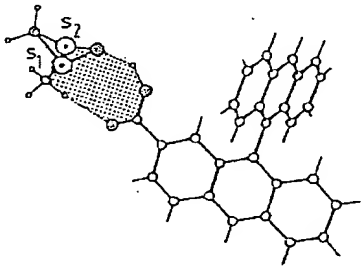
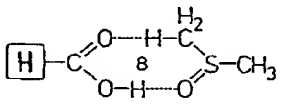
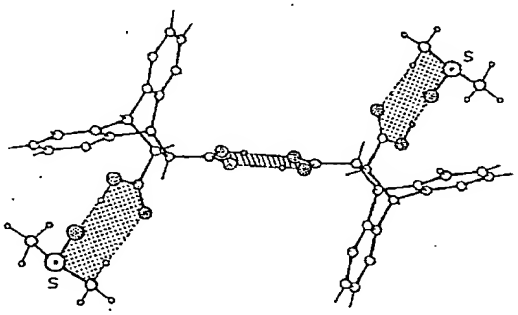
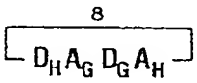
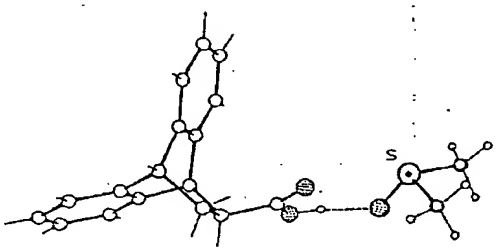
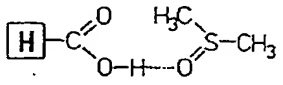
Roughly speaking, we may say that dimethylformamide acts in a way analogously to alcohols, with the difference of having its H-bond acceptor and donor functions in sterically distant sites compared to the —OH moiety. The prevailing recognition pattern can be subject to alterations, giving an individual touch to the associate in question, nevertheless it may be traced back to its characteristic form.

Dimethyl Sulfoxide (DMSO) as Guest Species

Examples of crystalline associates where dimethyl sulfoxide is involved as one of the heteromolecular constituents are known in an appreciable number[1]. Certainly the associate between dimethyl sulfoxide and trimesic acid [84] (cf. Chapter 5 in Vol. 140 of this series) is one of the important individual cases. Characteristic modes of association between the carboxylic hosts discussed here and dimethyl sulfoxide are illustrated in Fig. 24. Pertinent geometry data are listed in Tables 17 and 18. One may realize from Fig. 24 that the fundamental mode of association of the host acids *20*, *26*, *37*, and *41* is the formation of discrete H-bonded islands of host and (usually) one guest molecule.

The basic type I is represented by the 1:1 coordinatoclathrate of *20* · DMSO [85] (Fig. 24). It is seen that an O—H ... O interaction occurs between host and guest. Besides, one of the methyl C-atoms is proximal to the fixing —COOH thus forming a co-planar pseudo-ring arrangement of six non-H atoms (8-membered ring including

1 Fragment search in the Cambridge Crystallographic Data Base reveals 127 hits out of 42381 entries (state May 1985) having 'dimethyl sulfoxide' as the search query and allowing for the presence of metal atoms. In absence of such elements, the number of hits is reduced to 27.

Type and specification	Example
I	
	20 · DMSO (1:1)
	
	*26* · DMSO (1:1)
II	
	*37* · DMSO (1:1)
$D_H A_G$	

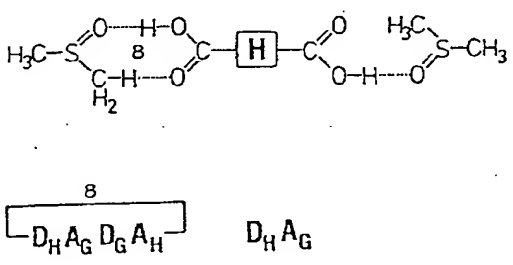
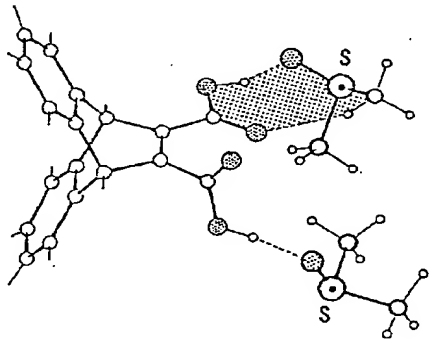
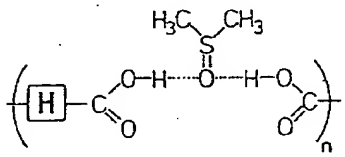
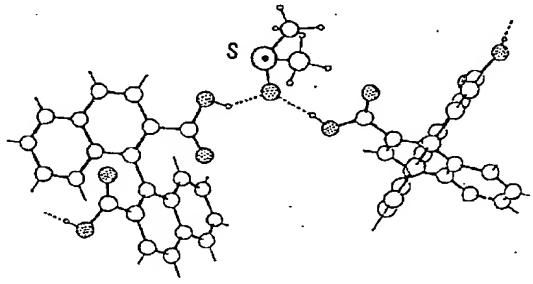
Type and specification	Example
IIIa 	 *41* · DMSO (1:2)
IIIb  $(D_H A_G A_G D_H)_n$	 *1* · DMSO (1:1)

Fig. 24. Binding modes of dimethyl sulfoxide to roof and scissor related mono- and dicarboxylic acids [71,82,85–87]. Discrete (type I), linear (type II) and discrete/linear (or polymeric, types III) classes are distinguished. The bold H stands for host, G for guest; A stands for acceptor, D for donor. H-bond rings coming from either host-guest or from host-host interactions (cf. *26* · DMSO) are indicated by different shading (dotted and hatched regions, respectively); single H-bonds are represented by a broken line. S1 and S2 in *20* · DMF (1:1) denote two disorder sites for the sulphur atom with comparable occupancy. Detail of H-bonding in the 1 · DMSO inclusion illustrate a minor part of the chain structure and counterfacing methyl group features (O atoms dotted; S atom marked with a bold dot; H atoms connected with non-heteroatoms are shown as sticks only, except for the guest molecules which are fully drawn)

Table 17. DMSO-distances, some close contact data, and calculated densities in the DMSO-inclusions of *1*, *20*, *26*, and *41* (cf. Fig. 24)

Cmpd	S—O	S—Cl	S—C2[a]	H—O ... O=S	C=O ... C (Me)	D_c
1	1.535(5)	1.678(16)	1.770(9)*	2.652(9) 2.635(8)	3.308(11)	1.326
20[b]	1.430(6) 1.396(9)	1.714(13) 1.720(14)	1.623(13)* 1.634(15)	2.634(7)	3.278(12)	1.312
26	1.503(3)	1.772(6)	1.767(4)*	2.606(3)	3.346(5)	1.338
41	1.522(3) 1.504(3)	1.773(4) 1.780(5)	1.770(5)* 1.783(5)	2.563(4) 2.562(3)	3.288(5) 3.383(5)	1.337

[a] Bond marked with * maintains the C atom involved in the C=O ... C (methyl) interaction. [b] Structure has a disordered DMSO molecule in the form of mirror-imaged overlap; hence its geometry data can be considered indicative only.

H). As shown, a disordered structural model was obtained for the guest. The model comprises two mirror-related guest molecules. The oxygen atom and the proximal methyl C-atom are practically overlapping the same atomic positions in both orientations. However, the sulphur atomic positions do not average in the X-ray data and show a nearly 50/50 occupancy. As indicated by the comparison of the respective bond distances and intra-associate contact distances of the DMSO molecule (Table 17), the effect of disorder is serious (e.g. the S=O distances appear abnormally short in the *20* · DMSO instance). This precludes the possibility of assessing interaction between the O atom of the carboxyl and a methyl of dimethyl sulfoxide.

Basically the same type I binding is found in the 1:1 coordinatoclathrate of *26* · DMSO [71] (Fig. 24). That is to say, the binding of the guest is characterized by the O—H ... O hydrogen bond and by the proximity of one of the methyl groups. Besides, the dimer formation of host *26* (cf. Fig. 23, type II) appears again. In these two type I cases, the oxygen atom of dimethyl sulfoxide in the inclusion acts as a single H-bond acceptor.

Table 18. H-bond dimensions in the dimethyl sulfoxide inclusions of *1*, *20*, *26*, and *41* (cf. Fig. 24)

Cmpd	D—H ... A	D ... A (Å)	H ... A (Å)	D—H (Å)	D—H ... A (deg)
1	O11—H11 ... O1d	2.652(9)	1.78	0.98	146
	O11'—H11' ... O1d	2.635(8)	1.70	0.99	155
	C2d—H2d3 ... O10'[a]	3.308(11)	2.27	1.08	161
20	O13—H13 ... O1d	2.634(7)			
	C2d—H2d ... O12[a,b]	3.278(13)	2.47	1.11	129
26	O15—H15 ... O1d	2.606(3)	1.65	0.97	167
	O18—H18 ... O17	2.629(3)	1.80	0.83	174
	C1d—H1d ... O14[a,b]	3.346(5)	2.38	1.08	148
41	O17—H17 ... O1d	2.563(4)	1.62	0.95	172
	O15—H15 ... O2d	2.562(3)	1.52	1.07	161
	C1d2—H121 ... O18[a]	3.288(5)	2.37	1.06	144

[a] Maintains a C—H ... O close contact. [b] Guest molecules disordered over two sites; hence these data may only be considered *cum grano salis*.

Another very recent example of a somewhat deviating association pattern is provided by the 1:1 coordinatoclathrate of the monoacid *37* with dimethyl sulfoxide [86] (Fig. 24, type II). Here the guest molecule is bound to the host by the aid of a single O—H ... O interaction and both methyls are placed further off from the —COOH group.

The structure of the related 1:2 inclusion compound of *41* [87] (Fig. 24, type III a) is constructed again in a slightly different way. It may be considered as a combination of the pure types I and II in a single island of the inclusion aggregate. Both oxygen atoms act as single acceptors of H-bonds. Probably due to steric crowding, only one of the guests is allowed to adopt a "proximal methyl group" configuration to its fixing —COOH. This pattern (termed as type III a in Fig. 24) tells us that there is a degree of flexibility in the way dimethyl sulfoxide is kept by the —COOH group, depending on, e.g. local (packing) conditions.

The 1:1 inclusion compound of *1* with dimethyl sulfoxide was studied [82] in order to broaden knowledge of the binding modes of *1* to different solvents. The preferred accommodation of dimethyl sulfoxide in competition experiments with other dipolar-aprotic solvents (e.g. acetonitrile, Table 2.) suggested some kind of a strong interaction. As shown in Fig. 24 (type III b), the crystal structure of *1* · DMSO is most appropriately described as a double-acceptor guest molecule pattern. Alternating enantiomers of *1* and intercalated dimethyl sulfoxide molecules are stacked to form H-bound infite chains (see Table 18 for geometry data). These chains are repeated in the crystal by a glide plane symmetry operator in the *ac* crystallographic plane. The structure shows that both the proximal methyl group (type I) and the single-acceptor (type II) patterns coexist in this crystal. Both types I and II are combined in a way to focus these features in one *guest* molecule. This is in contrast with type III a since in the latter case combination of types I and II applies to the relations with one *host* molecule. In fact, due to the chain-like nature of the H-bonds between guest and host molecules, it is not possible to discriminate between intra- and inter-associate relations any longer. A similar chain-like involvement of dimethyl sulfoxide has recently been found for an associate composed of dimethyl sulfoxide and the adduct of hexachloroacetone with water [88].

Four out of the five associates in our studies display 1:1 host:guest stoichiometry (those of *1*, *20*, *26*, and *37*). Only the corresponding inclusion of *41* has a 1:2 stoichiometry. This difference could be linked up with the altered orientation of the vicinal carboxyl groups.

Summing up, one may conclude that formulation of the rules with reference to molecular recognition of a dimethyl sulfoxide guest by carboxyl groups is problematic. This is due to the nature of the basic attachment to the acid group: it may be seen as a flexible one-point type of binding. Concerted packing effects and such a high degree of freedom easily yield somewhat varying structural motifs.

However, there still remain some basic similarities which may be summarized as follows:

— the sulfoxide oxygen acts as a H-bond acceptor (single or double one) and these H-bonds are usually strong ones (cf. Table 18);
— dimethyl sulfoxide is inclined to give a "counter-facing methyl group", i.e. one of the methyls of dimethyl sulfoxide faces the carbonyl oxygen of the guest-binding carboxyl group.

Hence, the dimethyl sulfoxide molecule in these examples tends to reach a possibly coplanar orientation with regard to the binding carboxyl group.

A more accurate model of this orientational behavior can not be deduced from the data at our disposal due to the known problems of locating reliable H-atom positions from electron-density maps based on room-temperature X-ray data. The appearance of structural disorder, especially manifested in the *20* · dimethyl sulfoxide inclusion, requires low-temperature data. Assumptions concerning the possibility of C(methyl)-H ... O interactions might perhaps be ascertained by other H-atom position sensitive methods (e.g. neutron diffraction). As indicated by some geometry parameters (Table 17), there are data which seem to correlate with such an assumption, while others are contradicting. Calculated densities which are also listed in Table 17 for some compounds parallel the observed disorder phenomenon of the *20* · DMSO aggregate having the lowest density among all dimethyl sulfoxide inclusions.

4.3 Inclusion Compounds Without Specific Binding Contacts Between Host and Guest: Apolar Molecules as Guest Species

So far, in accord with the original idea of coordinatoclathrate formation (see Sect. 2.2), such guest molecules which have been the main topic of the discussions could more or less intimately interact with the protic sensor groups of the host matrix. Another approach where an attempt is made to get rid of such dominant interactions between host and guest will be examined briefly in the following. One could expect from Fig. 8 (Sect. 2.2) that the more geometric dependent part of host-guest interactions will now gain in importance. Actually, remembering Sect. 2.1 of this chapter, one may expect that on meeting a proper guest, a host molecule supplied with functional groups could be able to form "true" or conventional clathrates (see Fig. 6a) as well. This way of thinking also prepares the ground for a kind of conscientious engineering of crystal structures based solely on the host shape. Corresponding ideas have been incorporated into the forthcoming discussion.

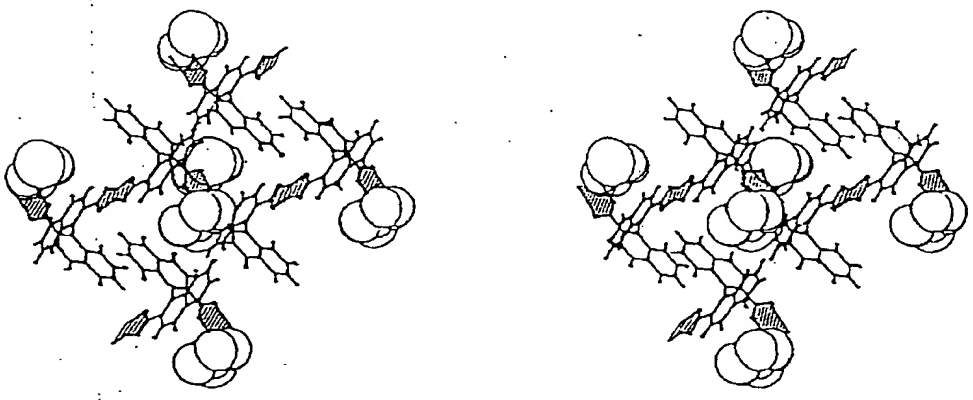


Fig. 25. Stereoscopic packing illustration of the *1* · bromobenzene (1:1) clathrate [82]. The guest molecules are shown by enlarged atomic radii (arbitrary values). H-bond rings coming from carboxylic group dimerization are indicated by hatching

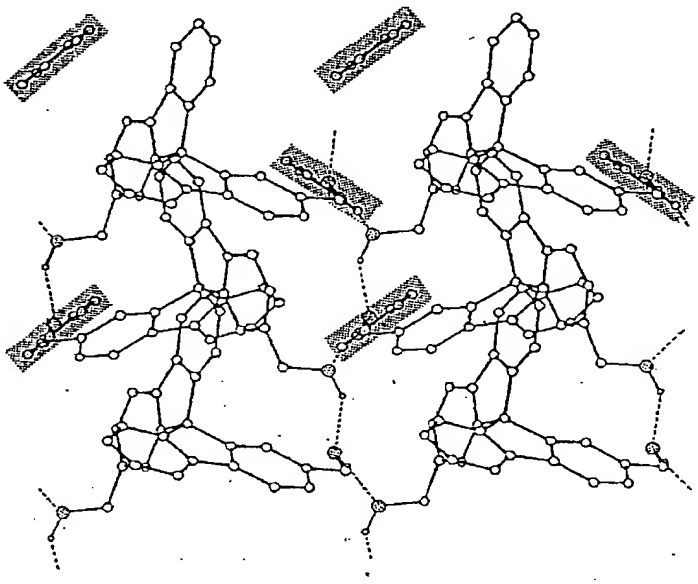


Fig. 26. Packing detail from the crystal structure of *24* · benzene (1:1) (H-bonds as broken lines; O atoms dotted; the guest molecules are marked by shading) (Adapted from Ref. 89)

We assume from Table 1 (Sect. 3.2.2) that the prototypical coordinatoclathrate host *1* forms indeed a crystalline 1:1 inclusion with bromobenzene. It is obvious, why the structure of this compound arose our curiosity. The result of the structural study [82] is shown in Fig. 25. As expected, bromobenze has no direct contacts to the encircling host matrix. It is located in channels formed between endless zigzag-like chains of host *1* with alternating chirality. The arrangement shown offers the possibility of having the guest molecule included in the apolar channels formed between such chains. Accordingly "true" clathrate formation characterized by strong host-host, but no direct host-guest contact has occurred.

Spatial accommodation of the guest evidently allows disordering of the guest molecule, another characteristic feature of "true" clathrates. This structure may serve as a general model for other possible inclusion compounds of *1* with apolar guests and also, in lack of the structure of the free host *1* (cf. Sect. 4.1), it may help to imagine a probable steric arrangement for that case.

Another example of the same building principle is found in the literature [89] for the *15*-analogous dialcoholic spiro host *24*, namely in its 1:1 inclusion compound with benzene (Fig. 26). The host molecules are bound into infinite zigzag chains by H-bonds and disordered benzene molecules appear interstitially placed between such chains.

Oddly enough, the 1:1 clathrate formed between 9,9′-bianthryl (*47*) and benzene has a very well ordered structure [64] (Fig. 27). The guest molecule has almost ideal geometry in this crystal. This is explained by the tight fit of the pairs of benzene guests into the environment maintained by the cross-shaped host (see also Sect. 4.4, Fig. 36). Unquestionably, this structure repeats basic characteristics except the functional groups of the species described before. However, unlike the aforementioned cases, both host-guest and host-host interactions are lacking here. Thus, in the strictest sense of classification (see Sect. 4 of Chapter 1 in Vol. 140), we deal with an example specified as (*a*) in Fig. 15 of Vol. 140, namely a "true" clathrate. The

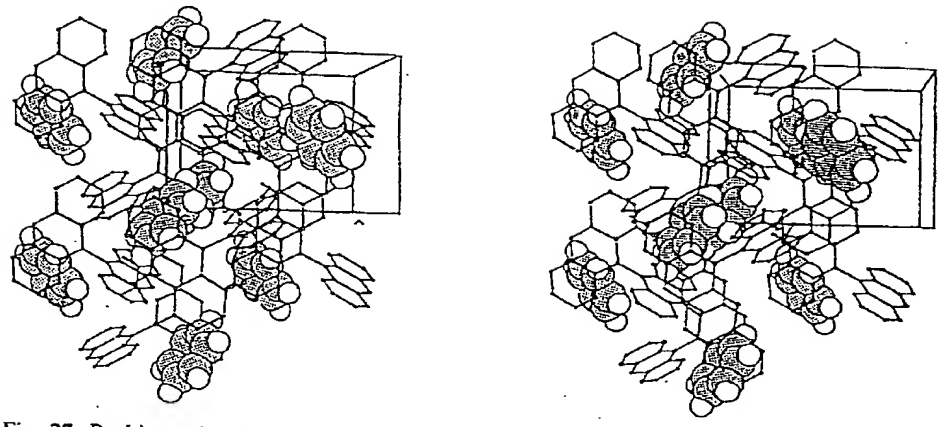


Fig. 27. Packing relations in the crystal structure of *47* · benzene (1:1) [64]. Stereo drawing of complementary stick style and space filling representations of host and guest molecules, respectively (atomic radii of the corresponding guest atoms in the space filling style are set to about half of their common van der Waals values; the H atoms of the host molecules are omitted)

former two clathrates belong to the "coordination-assisted host lattice"-type (Fig. 15b in Vol. 140), but none of all these represents a "coordinatoclathrate".

The family of "true" clathrates based on hydrocarbons only is further enriched by the inclusion compounds of *48* with benzene (1:1) and p-xylene (2:1) [90] (Table 19). Figure 28 illustrates the structure of *48* · benzene (1:1). The structure of the p-xylene clathrate shows intercalated guest molecules at centers of symmetry in the crystal lattice. Both clathrates are rather unstable at ambient temperatures and decompose easily, e.g. on exposure to X-rays (even in the presences of mother liquor). The *48* · p-xylene clathrate is unstable to such a degree that decomposition occurs at low temperature.

In accordance with this behavior, specific interactions between host and guest molecules are not indicated in the structures. The guest molecules take an inclination of approximately 45 degrees to both planes of the rectangular aromatic systems of

Table 19. Crystal data of pure hydrocarbon host-guest inclusions

Compound[a]	*47a*	*48a*	*48b*
Space group	$P2_1/n$	$P2_1/n$	$P2_1/c$
unit cell			
a (Å)	11.704	10.809	13.928
b (Å)	8.790	18.455	9.166
c (Å)	22.685	10.910	16.095
β (deg)	95.80	92.50	99.91
V (Å^3)	2321.57	2174.26	2024.09
Z	4	4	4
D_c (gcm^{-3})	1.237	1.205	1.212

[a] Designation: *47a* = *47* · benzene (1:1), *48a* = *48* · benzene (1:1), *48b* = *48* · p-xylene (2:1).

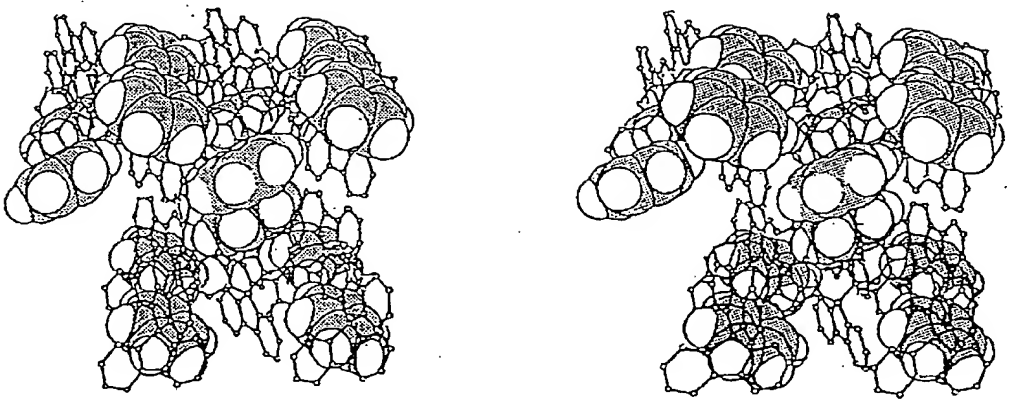


Fig. 28. Stereo view of the packing in the *48* · benzene (1 : 1) clathrate [90] (see notes of Fig. 27)

the hosts *47* and *48* in all three inclusions which excludes that π-π or similar interactions exist between the host and the guest partners.

4.4 Cavity Shapes: Steric Fit of Host-Guest Compounds

One of the aims of the crystallographic studies is to visualize the spatial conditions of non-H-bond type of interactions. Van der Waals forces (dispersion and exchange repulsion) and polarization are representatives of such interactive forces. They are governed by geometric features such as contact surfaces and volumes of the host and guest matrices.

The basic structure pattern which is noticed in the packing schemes of the crystalline inclusions between *1* and alcohols is a channel matrix formed by the host. The walls of these channels are hydrophobic in their main constitution, but they are regularly interrupted by protruding carboxyl groups where the guests bind via their polar endings (Fig. 29). Thus, depending on the lattice symmetry which is controlled by the guest shape, different arrangements of the polar/apolar segments with respect to the symmetry elements will exist. For the same reason, one may also observe that

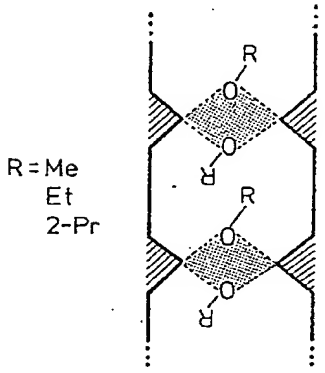


Fig. 29. Schematic representation of the longitudinal cross-section of the inclusion channel for the simple alcohol inclusions of *1* with MeOH, EtOH, and 2-PrOH [2]. Hatched triangles and dotted squares represent polar areas (cf. Fig. 19, type IIa), while the rest is of apolar property

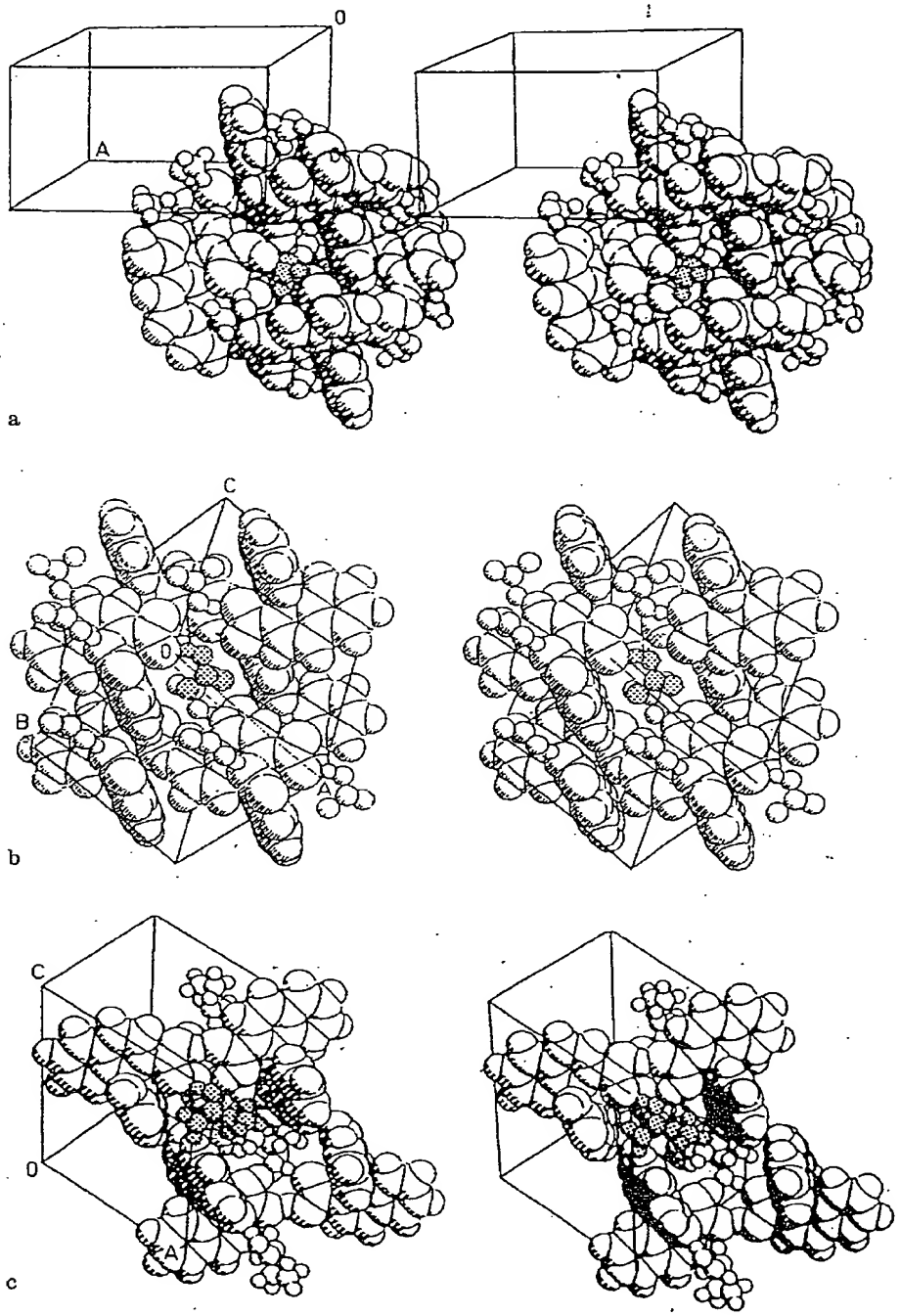


Fig. 30. Stereoscopic space filling illustrations of inclusion channels present in *1* · alcohol clathrates [2]. In each illustration, one of the guest molecules included in the channel is specified by shading (atoms of the guest molecules are shown with 20% of their van der Waals radii throughout these representations): (a) *1* · MeOH (1:2); (b) *1* · 2-PrOH (1:2) and *1* · EtOH (1:2). Due to isomorphism only the 2-PrOH structure is shown (guest H atoms are omitted for the sake of clarity); (c) *1* · 2-BuOH (1:1).

the size of the inclusion channel varies, although identical building blocks are used for creating H-bonds.

For instance, the arrangement of host molecules in the methanol inclusion of *1* (Fig. 30a) resembles the structure observed in the crystal of unsubstituted solvent-free 1,1'-binaphthyl *43* [72]. A difference between the basic packing rules in plain *43* and the methanol inclusion of *1* is in the following point: in case of the inclusion compound, the H-atoms at the far end of the host skeleton (with respect to the —COOH positions) approach closely the planes of neighboring aromatic rings lying nearly perpendicular to each other. In the crystal of 1,1'-binaphthyl, however, these H-atoms point to the lateral (mantle) atoms (e.g. at position 2) instead of the ring centres.

In the inclusion compounds of *1* with ethanol and isopropanol (Fig. 30b), the H-atoms under discussion are shifted even more outwards with respect to the neighboring naphthyl rings placed at right angles in the crystal space. This occurrence may also be seen as an opening of the inclusion tunnel which seems to be adapting itself to the steric requirements of the aliphatic portion of the guest molecule (cf. Figs. 30a and 30b).

In fact, the wall of the channel is lined with polar and apolar segments in a specific way. This is demonstrated by Figs. 31a and 31b showing that the polar segments are located in the corners of the channel, while the apolar ones make up the greater part of the wall. Hence the channel is tailored in a way that it corresponds to the characteristics of the substrate molecule. Hydrophobic portions (aliphatic tail of the alcohols) are placed into the hydrophobic region of the recepting channel while the hydrophilic groups (—OH functions) match the proper —COOH moieties protruding into this space (cf. Fig. 29).

A certain flexibility of this particular arrangement is obvious when considering the 2-butanol case of inclusion. As already discussed, the scheme of H-bonding changes here from a symmetric to an asymmetric ring system (cf. Fig. 19, types I vs. IIa). Nevertheless, another center of symmetry (placed between the aliphatic termini of related guest molecules) is retained, similarly to the lattices of the simpler alcohols mentioned above. The so-formed enlarged cavity around the 2-butanol guest (Fig. 30c) is still preserving the main characteristics of the former set-up. One of the polar

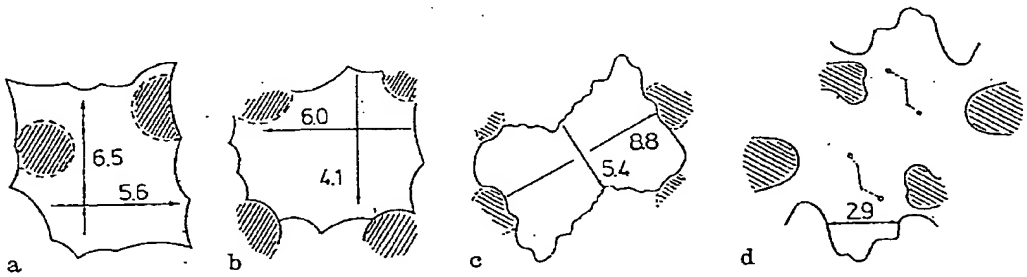


Fig. 31. Approximation of van der Waals cross-sections of inclusion channels in *1* · alcohol clathrates [2] (dimensions are in Å; hatched regions represent O atoms of the host matrix; continous solid lines indicate surfaces of apolar attribute): (a) *1* · MeOH (1:2) (approximately parallel to the $O_{(z)}$—$C_{(z)}$ vectors, cf. Fig. 17a); (b) *1* · 2-PrOH (1:2) (orientation as before); (c) *1* · 2-BuOH (1:1) (through a center of symmetry at 1,1/2,1/2, cf. Fig. 30c; non-zero electron density contours); (d) *1* · ethylene glycol (1:1) (in the plane of the C—C single bonds of a guest molecule, indicated by projected stick models; non-zero electron density contours)

centers (a coordinating oxygen of a carboxyl group) differs as it appears in the middle rather than in the corner of the channel (Fig. 31c). The increase of one dimension by approximately a factor of two (from 4.1 to 8.8 Å, see Fig. 31) follows the conservation of the pattern in Figs. 31a and 31b. The width of the channel in the height of the captived alcohol remains practically the same and is around 5.4–6 Å in these cases. Thus, these findings also indicate the ability of *1* to act in a systematically complementary way in order to build a stable heteromolecular crystal structure.

In the ethylene glycol inclusion of *1*, the channel structure cannot be detected any longer. An explanation is found in the fact that the gracile guest molecule,

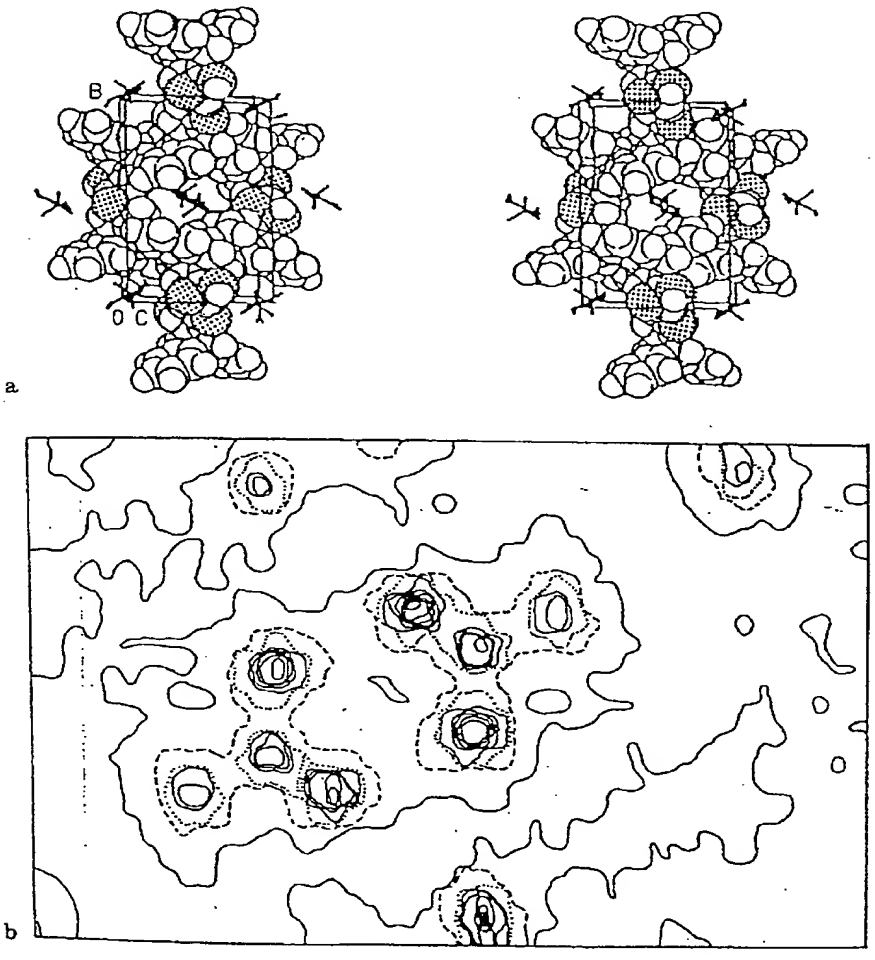


Fig. 32. Packing relations and steric fit of the *26* · acetic acid (1:1) clathrate (isomorphous with the corresponding propionic acid clathrate of *26*)[71]: (a) Stereoscopic packing illustration; acetic acid (shown in stick style) forms dimers in the tunnel running along the *c* crystal axis of the *26* host matrix (space filling representation, O atoms shaded). (b) Electron density contours in the plane of the acetic acid dimer[50]. First contour (solid line) is at 0.4 eÅ^{-3}, while subsequent ones are with arbitrary spacings of either 0.5 and 1 eÅ^{-3}. Density of the enclosing walls comes from C and H atoms of host molecules.

fully engaged in H-bonding, may approach the hydrophobic lap of the binaphthyl skeleton (Fig. 31d) thus resulting in a more compact structure. This is also indicated by the calculated density and the respective packing coefficient (0.77) for this associate which is the highest among the alcohol inclusions of *1* (see Table 11).

A further example of the steric fit and thus the conditions of the second rank interactions between host and guest is illustrated by the channel structure of the acid inclusions of *26* (see inclusion compound with acetic acid, Fig. 32a). The tunnel has a mostly hydrophobic character being made up mainly from the aromatic portions of the roof-shaped host molecule. We must note that this arrangement applies possibly for the acetic acid clathrate of *1* as well.

In Fig. 32b, showing the corresponding acetic acid clathrate of *26*, the cross-section of the electron density used to approximate von der Waals surfaces is taken in the plane of an acetic acid dimer [50]. It is revealed that by forming H-bonds only to another (symmetry related) guest acid and not to the —COOH groups of the host matrix, the roughly rectangular shaped dimer of the guest acids actually behaves as a certain hydrophobic species. This pattern is also observed in the isomorphous propionic acid clathrate of *26* and partly in the formic acid case as well. Therefore guest dimers fit the apolar channel ideally. Correspondingly, the present inclusion compounds between *26* and these acids may no longer be termed as coordinatoclathrates but "true" clathrates (cf. Sect. 2.1). Faster decomposition of the respective crystals on exposure to air is a macroscopic indication of this behavior.

As mentioned in Sect. 4.2.2, salt-type associates are the only representatives of the aggregates formed by *7*. In these crystals, the pyridinium cations appear surrounded by a rectangle-like environment maintained by *7*.

Following the order of discussion, the next type of guest molecules we examine briefly is the aprotic-dipolar class of solvents. A good example of the fit of guests and hosts is set in the packing of the *22* · DMF 1:2 inclusion [48] (Fig. 33). It shows that the orientation of the guest molecules is largely dictated by the rigid right angle shaped host framework. Such a guest orienting effect certainly contributes to the recognition pattern of the solvent joined with the effects of the sensor (—COOH) group (cf. Fig. 23, type Ia).

Another example of this solvent class can be studied in the case of the *20* · DMSO

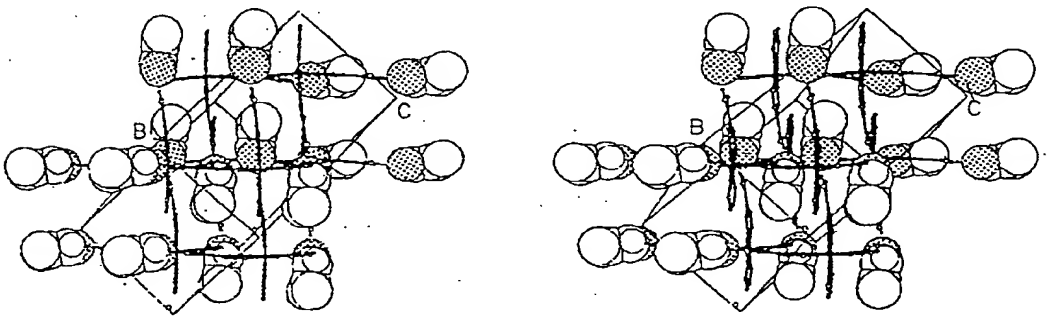


Fig. 33. Packing of the *22* · DMF clathrate [48] (stereo drawing). The joined orienting effect of the host lattice and of the sensor groups is illustrated showing the fit of the guest molecules (with 3/4 of the van der Waals radii of the composing atoms, O atoms shaded) to the host matrix (stick style)

1:1 inclusion [85] (Fig. 34). A part of a zigzag channel is seen with mostly apolar surfaces. Similarly to the channels of the alcohol inclusions of *1*, oxygen atoms of the —COOH groups appear to form polar (hydrophilic) corners. The drawing also shows ample space around the two centers of symmetry-related guest molecules in the middle pocket. This suggests a reasonable model for the disorder observed for the dimethyl sulfoxide atomic positions (cf. Fig. 24, type I, Sect. 4.2.3). Let us suppose that both DMSO-pyramids are oriented in the same way, say with their tips pointing upwards. Consequently the symmetry center which is still present in the drawing exactly in the middle of the box (at 1/2, 1/2, 1/2) would cease to exist in some of the unit cells. The empty space around the center at (1/2, 1/2, 1/2) in the crystal, enables the pyramid-shaped guest molecule to adopt both conformations with regard to the binding carboxyl group.

Another example to show that hydrophobic guest molecules favor disordering in the similarly tailored environment of the host matrix is seen in the bromobenzene inclusion of *1* [82]. The guest environment displayed in Fig. 35 by the contours of electron density both in and perpendicular to the plane of the aromatic guest molecule contains enough free space to allow for more than one orientation. In fact, it has been suggested by packing analysis [91] that there is a second orientation for the guest with ca. 1/3 population. This orientation may be derived by tilting the model from the main population by 180 degrees along an axis perpendicular to the longitudinal (the Br—C_{para}) axis of the molecule.

The cavity shapes in the case of pure hydrocarbon hosts may play an even more important role. This holds, e.g. for *47* in its inclusion compound with benzene (Fig. 36). The map of the electron density in the plane of the benzene molecule (Fig. 36a) suggests a tight envelope around the guest in the form of a hexagon. Benzene molecules are located in pairs in the crystal lattice (Figs. 36b and 36c), occupying almost completely closed cages with the edge lengths of ca. 6.5 × 7 × 12 Å.

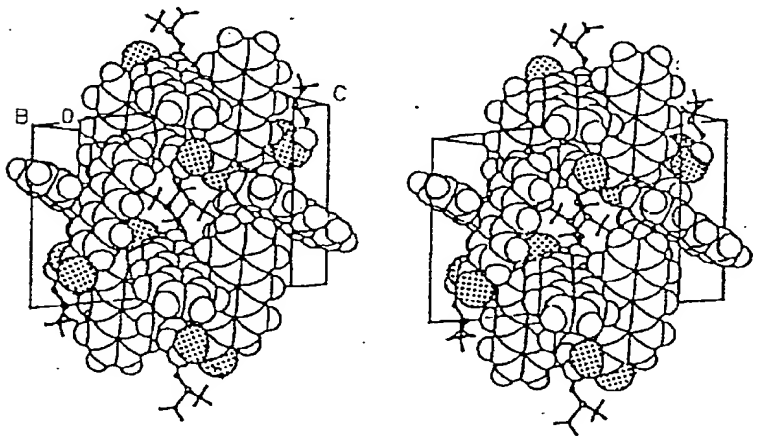


Fig. 34. Stereo drawing of the packing in the *20* · DMSO clathrate [85] (complementary space filling and stick style representations of host and guest molecules, respectively; O atoms of the host are shaded). Space around guest molecules in the center of the drawing, related by the symmetry center operator, indicates the opportunity for disorder

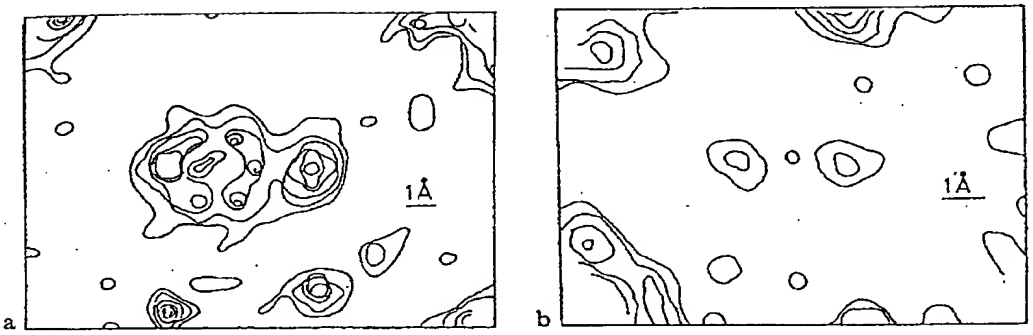


Fig. 35. Electron density distribution (arbitrary spacing) (a) in the plane of the guest molecule and (b) perpendicular to the longitudinal axis in *1* · bromobenzene (1:1) [82]. Second plane is bisecting through the middle of the Br—$C_{(\varepsilon)}$ bond of the main site. Plenty of empty space around the guest readily enables disordering

which are formed by the flat surfaces from eight contributing host molecules (cf. Fig. 27). The relative steric positioning of the benzene molecules arranged in pairs (Figs. 36b and 36c) suggests that base stacking between them does not exist. Figures 36b and 36c also reflect suitable conditions for the pairs of benzenes in the host cage by indicating dimensions. The cage structure of the host matrix and the extremely good spatial fit between hosts and guest are certainly responsible of the pronounced selectivity behavior of *47* and for the remarkably high thermal stability of this particular inclusion compound (see Sect. 3.5).

4.5 Interrelations Attributable to Special Host and Guest Features

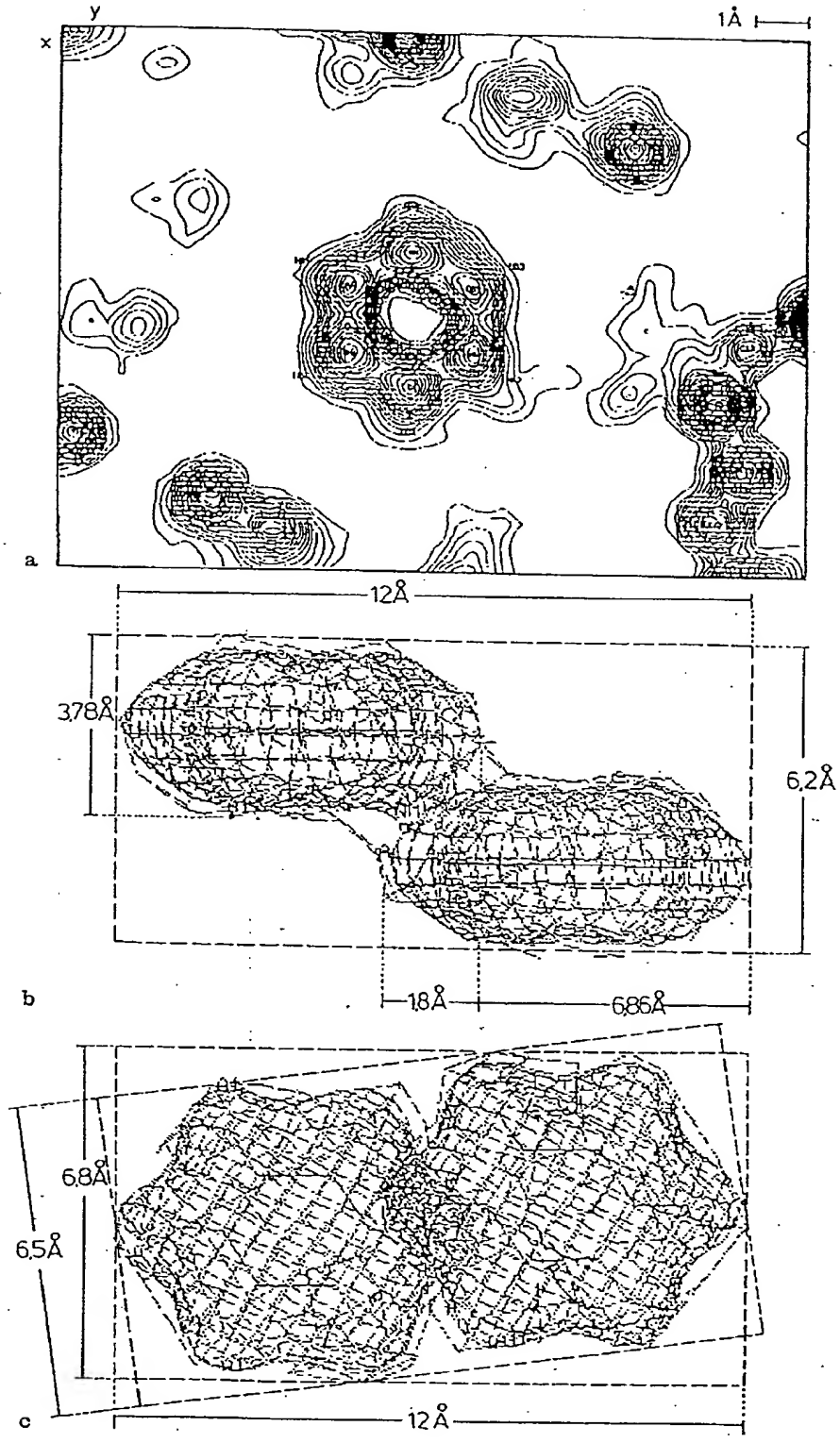
With reference to hosts and a guest, molecular assemblies have to conform to certain circumstances, generally called complementary relationships. They involve both steric and electronic terms. The objects may be achieved by the use of properly chosen sensor groups and by a suitably tailored basic skeleton as exemplified by the present scissor- or roof-shaped host molecules. From the point of view of the introductory thoughts of this chapter (cf. Sect. 3.1), it is a matter of consideration to see how consistent the "scissor" or the "roof" simile is in the light of crystal structures.

4.5.1 Shape and Symmetry Considerations: Dihedral Angles of Host Compounds

The obvious thing to do is to establish a kind of link, if any exists, between the various host molecules which may seem to differ principally at first sight. Examination of hidden similarities also throws light upon possible conceptual relations and may prove useful for the future.

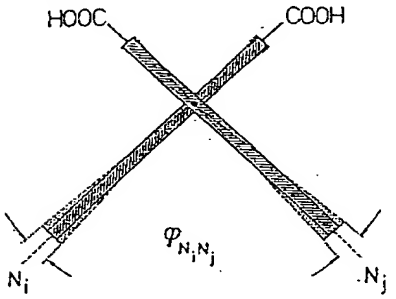
Shape of Host 1

As a general descriptor of the molecular shape of *1*, one may consider the dihedral angle between the chemically bound naphthalene moieties. Data of this parameter are listed in Table 20 for the studied inclusion compounds of *1* combined with a scheme that

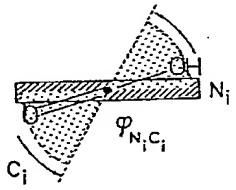

y
x
1Å
a
12Å
3.78Å
6.2Å
b
1.8Å
6.86Å
6.8Å
6.5Å
c
12Å

highlights the basic shape descriptors used in the following treatment. Characteristic shapes of the host molecule involving the aggregates of protic, aprotic-dipolar, and apolar guests are shown by selected examples for each class of compounds (Fig. 37).

Table 20. Shape of host *1* in its crystal inclusions as characterized by the virtue of dihedral angles. Attached diagram explains the angle designations[a]



a



b

Compound[b]	N_i/N_j	N_i/C_i		C_i/C_j
1a	92.2	7.2	6.0	84.7
1b	85.3	8.5	8.5	90.0
1c	86.3	17.2	17.2	91.6
1d	89.6	7.7	2.9	85.2
	87.3	1.1	6.8	87.2
1e	89.1	25.3	14.9	82.5
1f	86.0	10.8	29.5	80.8
1e	92.0	19.8	11.5	76.1
1h	92.5	10.4	3.1	87.3
1i	98.1	9.9	33.3	74.3
1j	93.1	2.9	15.0	91.7
	87.3	25.6	0.1	73.9
1k	92.2	17.2	4.0	96.9
1l	81.4	50.8[c]	60.7[c]	71.7
1m	87.7	25.4	34.8[c]	51.9[c]
Mean[d]	89.3(4.1)	11.9(8.3)		83.9(7.7)

[a] Planes N_i, N_j are the planes of the naphthyl rings (10 atoms); planes C_i, C_j are the planes of the —COOH groups (3 atoms). (Dihedral angles calculated by Chem X, Ref. 139). Mean values include 15, 26, and 14 data, respectively. [b] Designation: *1a–1g* see table 11; *1h* = *1* · DMF (1:2), *1i* = *1* · DMSO (1:1), *1j* = *1* · acetic acid (2:3), *1k* = *1* · bromobenzene (1:1), *1l* = *1* · imidazole · H_2O (1:1:2), *1m* = *1* · imidazole (1:1). [c] Data not included in the mean value. [d] R.m.s.d. in parentheses.

◀

Fig. 36. Spatial fit between host and guest in *47* · benzene (1:1) (see Ref. 64): (a) Electron density in the mean plane of a benzene revealing the encasing hexagonal environment aroung the guest; and (b) and (c) van der Waals surfaces of the dimeric benzene units as seen in Fig. 27 (indicated dimensions were calculated by the aid of the CHEM X program system, see Ref. 139). The lack of extensive-enough overlapping to yield in pi-pi interactions is visible from this drawing

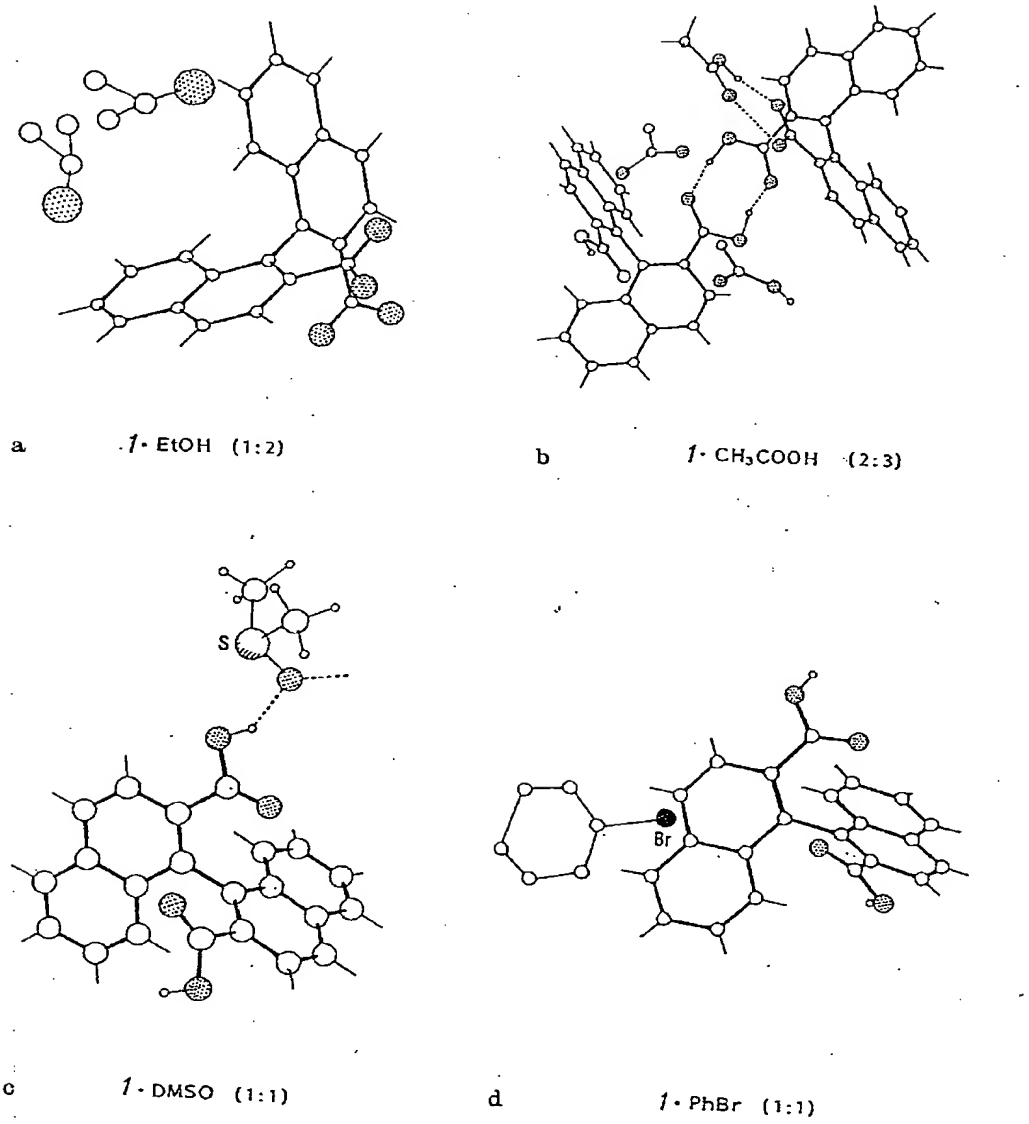


Fig. 37. Shape of host molecule *1* in some characteristic inclusion compounds [2, 79, 82] (a–d), (H-bonds are indicated as broken lines; O atoms dotted; H atoms connected with non-heteroatoms of the host are shown as sticks only; disordered terminal methyl groups are found for EtOH)

We observe a rather narrow distribution in the alignment of the naphthyl planes which lie nearly at right angle to each other [mean value 89.3(4.1)°], with a slight variation only (see Table 20) showing that this molecule has an almost stable shape in the crystal structures. It is possible to draw an interesting comparison with the same parameter found for some related compounds containing the binaphthyl moiety [45, 60, 61, 72, 73, 92–99]. In these structures, the values vary between 68 and 111° indicating that this dihedral angle may be subject to alteration due to environmental effects.

Another characteristic feature associated with the structure of host molecule *1* is the inclination angle of the —COOH groups to their anchoring naphtyl moiety. The mean value of this quantity and its r.m.s.d [11.9(8.3)°] obtained from the different inclusions show a moderate inclination to the aromatic moiety and a somewhat enhanced scattering of the data (Table 20). The differing steric and electronic needs of the particular guest species seem to be reflected mainly in this parameter. As a general tendency one may deduce: the bulkier (more branched) a guest is, the larger this dihedral angle becomes (cf. Table 20.)

As a third shape descriptor of *1*, the dihedral angle between the two —COOH groups is considered. The mean value [83.9(7.7)°] (Table 20) reflects moderate deviation of these moieties from a roughly perpendicular steric positioning with respect to each other.

Shape of Host 7

Chemical facts in the case of host *7* point to rigorous steric dependence of associate formation. Though the number of the available data is rather limited, their mean values seem to be in conformity with such an assumption. The dihedral angles between the characteristic planes in these structures show that the inclination of the naphthyl planes to each other varies in a range between 58 and 68° with a mean value of 64.2(3.5)° (Table 21). The inclination angles of the —COOH groups to their respective naphthyl moiety lie also in a relatively narrow range with a mean value of 53.5(5.1)° deviating significantly from *1* (cf. Table 20) and is certainly involved in explaining the different inclusion behavior between *1* and *7*. A similar value for this angle is found, however, in the imidazole associates of *1* (see Sect. 5). The —COOH functions are at an angle of 73.8(2.9)° to each other. Two examples shown in Fig. 38 represent the particular host shape of the free [68] and of the pyridine associated form [80].

Shape of Host 26

Selected examples illustrating the shape of host *26* under various conditions are given in Figs. 39a–39c. The first parameter we choose to characterize the shape of *26* is the inclination angle of the phenyl rings readable at the gable of the roof-shaped molecule (graphical representation in Table 22). It indicates little variation [see

Table 21. Shape characteristics of host *7*

Compound[a]	N_i/N_j[b]	N_i/C_i		C_i/C_j
7	58.3	45.0	45.0	78.7
7a	64.2	53.6	56.7	73.0
7b	67.5	61.1	54.0	71.1
7c	65.1	54.5	57.0	72.5
7d	65.8	56.5	51.6	73.6
Mean[c]	64.2(3.5)	53.5(5.1)		73.8(2.9)

[a] For designation see Table 14. [b] Details in Table 20. [c] R.m.s.d. in parentheses.

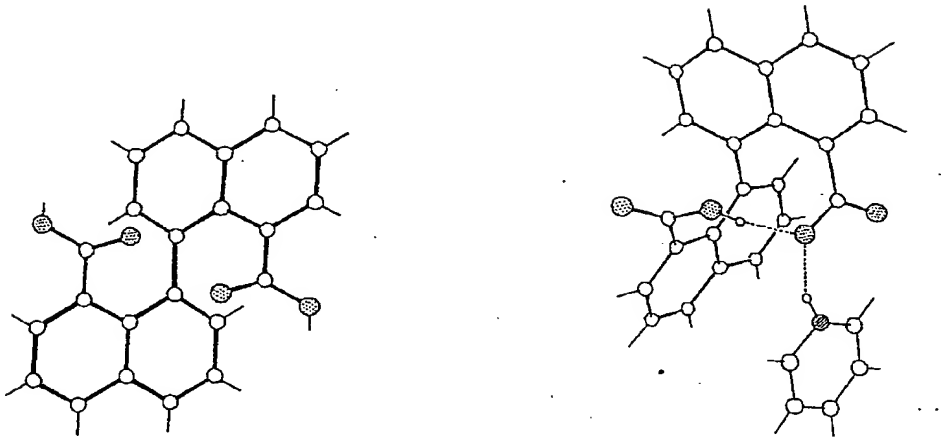


Fig. 38. Geometry of *7*: (a) in the free state (unsolvated crystal) and (b) in a typical salt-type associate (*7* · pyridine, 1:1) (H-bonds are indicated as broken lines; O atoms dotted, N atoms hatched; H atoms connected with nonheteroatoms are shown as sticks only)[80]

Table 22, mean value 123.9(2.4)°], as expected of a molecule with highly rigid constitution. Rigidity of the basic skeleton of *26* is also reflected in the symmetrical displacement of the finial (the bridging ethano-moiety) with respect to the roof-planes [mean angle 62.0(2.1)°]. The carboxyl groups show also little variation in their spatial arrangement with respect to the finial, generally they adopt a tilted arrangement with a mean angle of 50.9(6.9)°. The mutual displacement of the acid groups, with one exception, leads to a nearly perpendicular arrangement with a mean value of 86.5(8.3)° for this angle. The exceptional case is for one of the free host molecules (out of the two in the asymmetric unit, cf. Table 22) which is probably forced into this alignment on the formation of the dimer.

It is most interesting to compare these data to the respective angles obtained for *41* in its dimethyl sulfoxide inclusion compound (Table 22 and Fig. 39d). One finds a certain feature departing from those noticed above. It concerns the angles of the —COOH groups to the finial (an etheno-moiety in *41*) which now have values pointing to a coplanar/perpendicular positioning of the acidic groups with reference to the etheno-segment. However, the nearly perpendicular arrangement of the —COOH functions with respect to each other is still maintained in *41*. It seems to reflect a favored way of arranging the two carboxylic groups in space in this particular family of host compounds.

Generalization of the Shape and Symmetry of Coordinatoclathrate Hosts

The scheme of the most common hosts in this study (Fig. 40) shows that they can be considered as a homologous series of dicarboxylic acids of different chain length (1,2-, 1,4-, 1,6-, and 1,7-diacids, respectively) involving an essentially rigid central segment. A summary substantiates the similarity of the mean angles of *1*, *7*, and *26* (Table 23) and a more or less steady shape of these host molecules in the free state

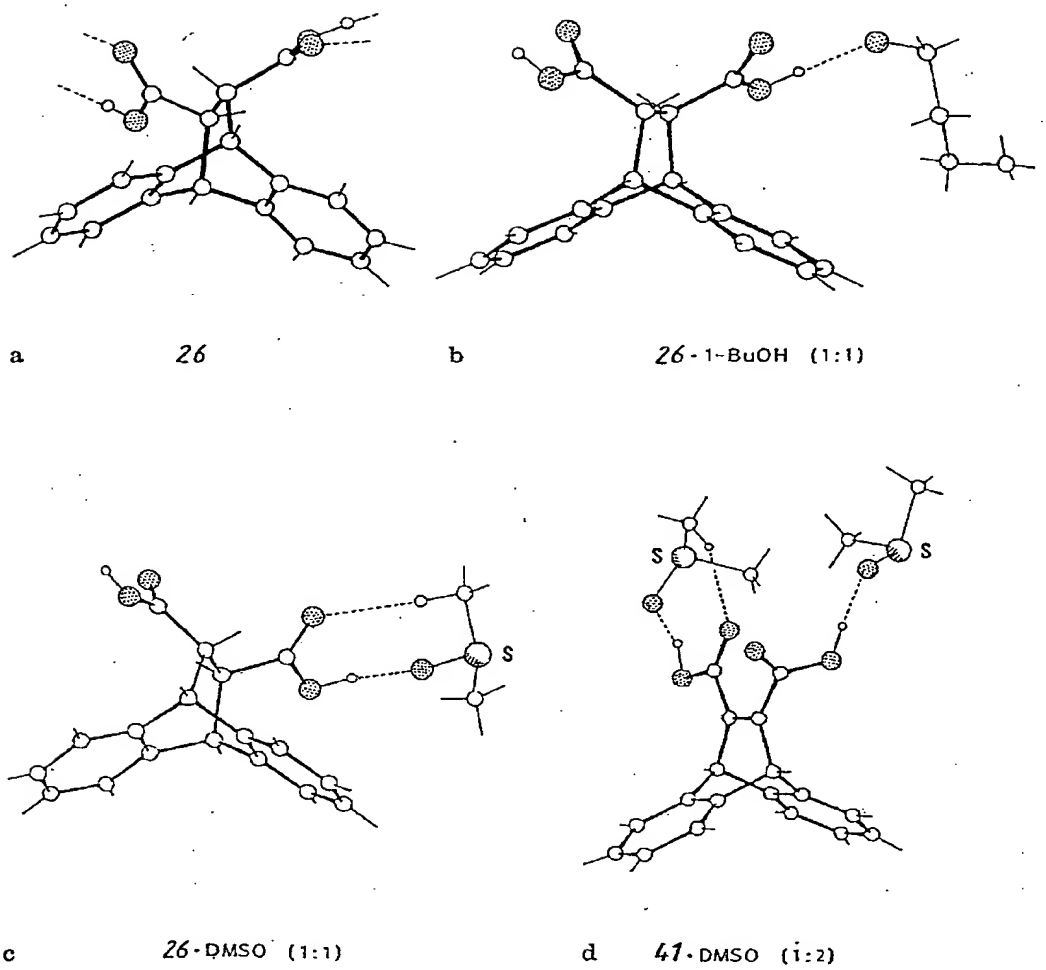


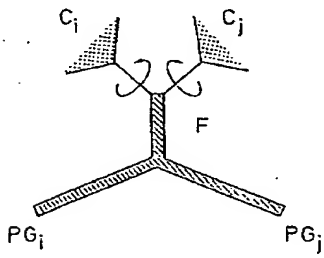
Fig. 39. Geometry of *26* and of the related host *41* in the free state (unsolvated crystal) and in some characteristic inclusion compounds [71] (a–d) (H-bonds are indicated as broken lines; O atoms dotted; H atoms connected with non-heteroatoms are shown as sticks only)

and in their inclusions (see Tables 20–22) as well. Even the conformation of the mobile —COOH groups shows only a narrow range of data.

It can be concluded from the X-ray data that these hosts possess a rigid or semirigid molecular skeleton. The importance of a preformed receptor shape is well documented in the chemistry of the artificial [100,101] and natural [102] receptors. For example, a preformed receptor was found to be helpful in reducing the activation energy for complexation that contributes to the recognition of a proper substrate [100,101]. Such an essentially entropic effect through the preorganization of a binding site may also be effective in the inclusion formation of the scissor- and roof-shaped host molecules discussed here.

Another remarkable feature of most of the inclusion hosts of this chapter is that they possess at least approximately (i.e. noncrystallographic) twofold symmetry.

Table 22. Shape of hosts *26* and *41* in their crystal inclusions, or in the free state, as characterized by inclination angles of some planes. Attached drawing explains definition of the interplanar angles (deg)[a]



Cmpd[b]	PG_i/PG_j	PG_i/F	PG_j/F	F/C_i	F/C_j	C_i/C_j
	126.2	61.9	64.4	51.0	64.7	65.1[c]
26	123.6	62.7	60.9	51.5	49.9	83.0
26a	122.3	60.4	62.0	50.5	46.1	90.2
26b	122.0	61.9	60.1	60.2	45.5	75.7
26c	128.3	63.5	64.8	54.0	43.0	85.9
26d	121.2	57.9	63.7	43.4	55.3	84.2
26e	125.1	65.2	60.0	61.5	41.4	102.7
26f	122.5	59.5	63.1	52.0	44.8	83.8
Mean[d]	123.9(2.4)	62.0(2.1)		50.9(6.9)		86.5(8.3)
41a	117.1	60.3	56.8	7.6	85.3	95.3

[a] Planes PG_i, PG_j are the planes of phenyl rings forming the gable (6 atoms); plane F is the plane of the finial (4 atoms); planes C_i, C_j are the planes of the —COOH groups. (Dihedral angles calculated by Chem X, Ref. 139). [b] Designation: *26a–26d* see Table 13, *26e* = *26* · DMF (1:1), *26f* = *26* · DMSO (1:1), *41a* = *41* · DMSO (1:2). [c] Omitted from the mean value; if included, the mean for C_iC_j becomes 83.8(10.8)°. [d] R.m.s.d. in parentheses.

In a few instances this property becomes ideal, i.e. there is a coincidence of molecular and twofold crystallographic symmetry (see inclusion compounds *1* · EtOH, *1* · 2-PrOH, and *22* · DMF). The presence of such an internal symmetry has been recognized to bear general consequences on the constitution of crystal lattices [27,103], in particular for dicarboxylic acids [102] and hence applies also for the diacids under consideration. Actually the internal C_2 molecular symmetry axis of the host molecules is oriented perpendicular to *c* or *n* glide planes in the crystal lattices. This is the prominent feature of all the crystal structures of this study, whenever the space group permits the presence of such glide planes. The propagation of the chain build-up of H-bond fused molecules in several of the crystals behaves according to this rule and the spatial positioning of the carboxyl functions with respect to the internal symmetry element.

As shown in Fig. 40, all of the hosts have their acidic groups placed on the same side in respect of the internal C_2 symmetry counterfacing the hydrophobic region of the molecules in question. In other words, they could be described as having a "cisoid" or "Z" conformation.

It has also been noted that self-complementary objects must follow twofold sym-

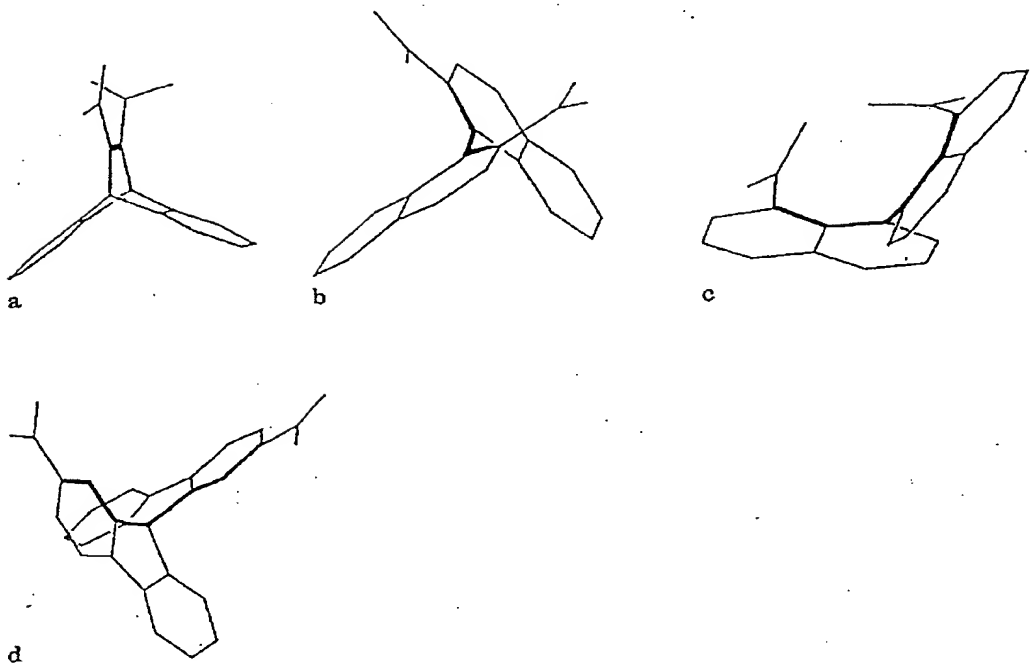


Fig. 40. Relation between host molecules of this study and dicarboxylic acids of different chain length (specified by heavy lines in the skeletal drawings): (a) (*41*), (b) (*1*), (c) (*7*), and (d) (*22*) correspond to 1,2-, 1,4-, 1,6-, and 1,7-diacids, respectively [67a]

metry on their contact surfaces [105]. Minor deviations from such a molecular symmetry in a crystal cause local breakdowns of the close-packing principle which remains one of the governing principles of the solid associate formation (cf. Ref. 27) and may give rise to the appearance of voids filled advantageously with guest species. Apparently gross violation of this internal molecular symmetry may reduce the ability of inclusion formation as shown for e.g. *38* and to some extent for *40*.

4.5.2 Effects Due to the Amphiphilic Nature of Host Compounds

The tendency of organic molecules to achieve the closest possible packing arrangement has been substantiated by many examples [27,103,106]. The packing coefficients (C_k)

Table 23. Summary of shape characteristics for hosts *1*, *7*, and *26* (mean values of dihedral and inclination angles, deg, with their r.m.s.d.)[a]

Host	N_i/N_j	N_i/C_i	C_i/C_j
1	89.3(4.1)	11.9(8.3)	83.9(7.7)
7	64.2(3.5)	53.5(5.1)	73.8(2.9)
26	123.9(2.4)	50.9(6.9)	86.5(8.3)

[a] N_i, N_j are the planes of the aromatics (10 atoms for *1* and *7*, 6 atoms for *26*); C_i, C_j are the planes for the —COOH groups. (Plane angles calculated by the aid of Chem X, Ref. 139).

of the alcohol inclusion of *1* range between 0.71 and 0.77 (Table 11) thus falling close to the expected normal range [27,103,106]. The segregation of hydrophilic regions in the crystals, as visualized in Figs. 29–31, indicates that there are regions in the crystals linked *via* strong H-bonds (hydrophilic interactions), on the one hand, and other less interacting areas on the other hand. These latter parts of the lattices are subject to weak intermolecular forces (e.g. dispersion) and enable the guest molecules in the respective portion to be statistically distributed in space (i.e. a disordered crystal lattice results).

Another simple parameter which reflects the tightness of crystal packing (cf. Sect. 4.4) is the calculated density (D_c). The data of D_c for the alcohol inclusions of *1* (Table 11, Sect. 4.2.1) indicate a slightly different compactness of the crystal structures. The extent of the disorder observed in the aliphatic part of some guest molecules seems to be correlated with this simple quantity. For example, the somewhat lower density of *1* · EtOH with respect to the nearly identically built structure of *1* · MeOH (cf. Sect. 4.2.1) indicates more space in the crystal of the ethanol inclusion. Thus, disordering of the terminal methyl group of the ethanol guest is possible. This property is even more pronounced for *1* · 2-PrOH. The resolved disorder sites for the methyl termini in the latter two guest molecules correspond to positions rotated approximately 60 degrees apart from each other. In the case of the more extended branched alcohols (see *1* · 2-BuOH and *1* · t-BuOH), the degree of disorder is somewhat slighter and is mainly indicated by the unreasonably short terminal C—C (methyl) distances [2]. The highest density in this series of compounds found for the inclusion of *1* with ethylene glycol indicates a closely packed structure (see. Sect. 4.4).

Summing up, the density data and the slight variation of the seemingly normal packing coefficients (Table 11) may be rationalized in terms of the observed disorder pattern. It means that there are regions of different compactness in some of these crystals. This becomes visible in those instances where the repulsive forces are somewhat more pronounced due to the less cooperative aliphatic moieties in the respective guests (cf. inclusion compounds of *1* with EtOH, 2-PrOH, 2-BuOH, t-BuOH, and ethylene glycol). These structures illustrate how the ideas put forward in Sect. 3.1 are verified in the crystals. The inclusions of other hosts (*20*, *26*) also exhibit such properties: matching of regions with proper characteristics and formation of a complementary host matrix to the respective guest volume.

4.5.3 Stoichiometry and Other Thermodynamics Related Effects

Stoichiometry is just one of the consequences of the fitting requirements between a guest molecule and a host matrix. It is important to recall that the meaning of stoichiometry being used to describe the real association nature of heteromolecular aggregates (cf. Chapter 1 in Vol. 140 of this series) might be somewhat different and more extended with regard to the common usage of the term. In this sense it is applied to describe the structural conditions of aggregate formation ("building block stoichiometry"). It obviously influences kinetically controlled events. As such, it may exert a certain influence on the selectivity pattern of a given host molecule towards different solvents (cf. Table 2 in Sect. 3.2.4). Naturally, selectivity is further controlled by enthalpy (e.g. strength of H-bonding in the crystal of an aggregate) and entropy effects.

An example of the contribution of the latter, originating from the properties of such systems, is obvious from the frequent appearance of statistical disorder in the inclusion compounds (cf. Sect. 4.5.2). Let us consider a several-component system (a host matrix made up of a few molecules and possibly already bound guest molecules and two different solvent molecules). The small (0.4 kJ/mol) preference in the Gibbs free energy of *1* · EtOH (or *1* · 2-PrOH) over a single conformation in the crystal structure [2] may be a relevant factor in steering such a system towards an equilibrium of slightly lower energy, as compared to a respectively non-productive case, e.g. *1* · MeOH.

Naturally selectivity in a several-component system is primarily influenced by rather strong effects such as the presence or absence of strong H-bonding, but possibly also by much weaker interactions (e.g. of C—H ... O type). In this regard, it is interesting to note the similarity between the selectivity exerted by such simple inclusion hosts, e.g. *1*, and chiral recognition [103]. In both cases, weak interactions are of decisive importance in the final outcome of the experiments. Entropic effects have been demonstrated to play a fundamental role in enzymatic reactions [102, 107]. Conceptual similarity of inclusion compounds to more complicated associates is underlined thereby.

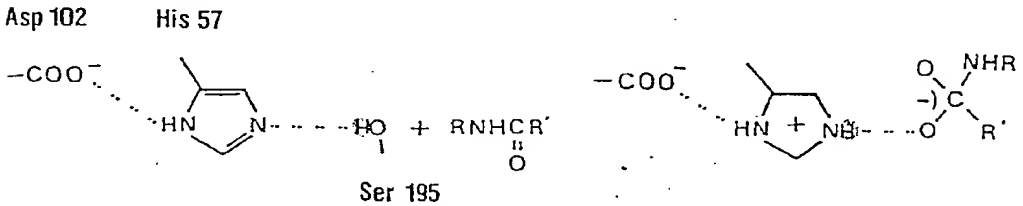
5 Coordinatoclathrates in Active Site Modelling of Protease Enzymes: Associates of *1* with Imidazole

As we saw in the previous sections, inclusion compounds have many structural properties which relate them to other systems based on the hierarchy of non-bound interactions, like enzymes or enzyme-substrate complexes. As a matter of fact, most of the so-called "artificial enzymes" are based on well-known host molecules (e.g. β-cyclodextrin) and are designed to act partly on such bases [108, 109]. Most of these models, however, take advantage of the inclusion (intra-host encapsulation) phenomena. Construction of proper covalently bound model molecules is a formidable task for the synthetic chemist [110]. Therefore, any kind of advance towards such a goal is welcomed.

Attemps at creating non-covalent models is a logical choice in this sense [111]. Many of the features of the coordinatoclathrates relate them to more complicated associates of biological molecules. As demonstrated in the preceding sections, simple hosts, like *1*, are able to maintain extended H-bound loops ("tertiary" structure formation), show in some cases nearly perfect selectivity (substrate specificity, cf. Sect. 3.2.4), and display entropic effects in their associates. Crystal growth and dissolution has also been shown to be dependent on the presence of chiroselective *inhibitors* [112]. Thus, apart from the former *static* analogies, one may find *dynamic* relationships as well. All these observations may be explained by the simple fact that the organizing forces are of the same type and approximate magnitude both for biological assemblies and for the crystals of simple organic molecules. As a consequence, the packing densities of biological assemblies (e.g. enzyme-substrate complexes) and organic crystals are also close to one another [113]. Proving by evidence, the possible similarity of simple crystal structures to the much more complicated network in protein molecules is a challenging task for the future.

5.1 Crystalline Associate of *1* with Imidazole and Water (1:1:2) [*1* · Im · 2 H_2O]

The outstanding inclusion ability and the carboxylic functions of host *1* raised the idea of co-crystallizing it with imidazole (Im) which, due to its versatile nature [114], is one of the frequently used components in enzyme active sites, generally presented by histidine. Formally, a system made of imidazole and an acid component may mimic two essential components of the so-called catalytic triad of the serine protease family of enzymes: the acid function of Asp102 and the imidazole nucleus of His57 [115] (trypsin sequence numbering). The third (albeit essential) component of the triad corresponding to the alcohol function of Ser195 was not considered in this attempt. This family of enzymes is of prime importance in metabolitic processes. By virtue of the (— + —) charge distribution of the aforementioned Asp-His-Ser triad, they are able to cleave peptide (or ester) bonds [116] (Scheme 1).



Scheme 1. Formation of the tetrahedral intermediate with the development of (— + —) charge distribution in serine proteases [111]

On intuition, a minute amount of water was added to the solvent (ethyl acetate) in the first crystallization experiment containing a molar excess of imidazole corresponding to *1*. Regularly shaped crystals were formed within one hour. Such a crystal, subjected to X-ray analysis, has the structure as shown in Fig. 41 [111]. Apart from the formation of the expected salt-type associate (carboxylate-imidazolium ion pair, cf. Sect. 4.2.2), two water molecules are present in the asymmetric unit of the crystal structure. This fact called our attention again to the family of serine protease enzymes, where water molecules are reported as being located in the close vicinity of the active sites [115–120].

5.1.1 Intra-associate Relation in *1* · Im · 2 H_2O

As already demonstrated (see Sect. 4.5.1), *1* displays a characteristic shape in its inclusions even with respect to the inclination angle of the carboxyl groups to their naphthyl planes. Coplanarity of these moieties depends partly on the bulkiness of the substrate molecule, however, the interplanar angle usually does not exceed 30° [mean value 11.9(8.3)°, Table 20].

This property is contrary to the present case, where the dihedral angle approaches a *gauche* arrangement of the naphthyl and carboxyl/carboxylate moieties with respect to each other (dihedral angles 50.8 and 60.7°, Table 20). Another remarkable conformational difference in the geometry of *1* is the presence of an *intra*molecular H-bridge between the carboxyl and carboxylate groups with the aid of a *cis* positioned O—H bond. A similar disposition of bonds has been observed in the case of the salt-type inclusion aggregates of *7* (cf. Sect. 4.2.2). It must be noted that the present arrangement is not the common mode of the steric alignment of this bond [104].

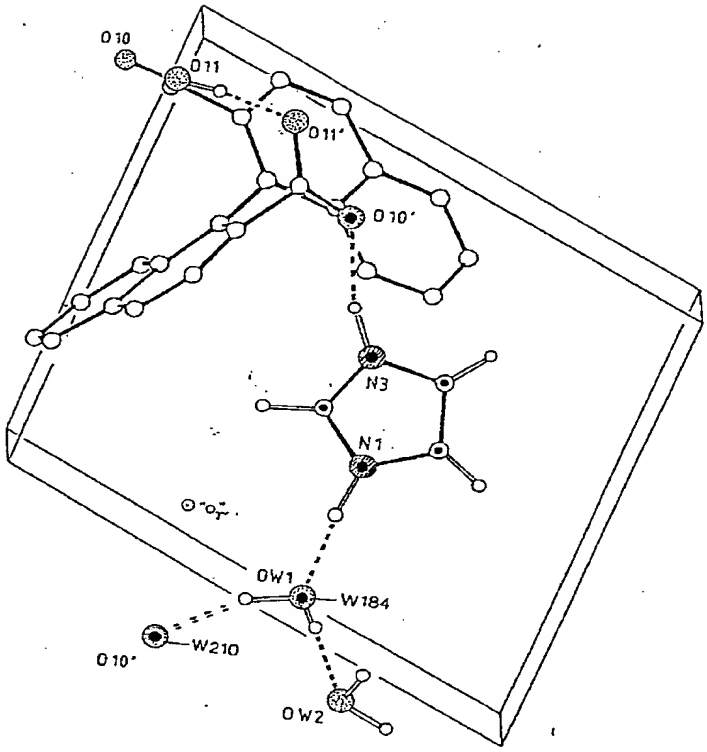


Fig. 41. Crystal structure of the *1*-imidazolium dihydrate associate [111] (O atoms dotted, N atoms hatched) showing intra-associate H-bonds (broken lines) and the resulting coinciding atomic sites from the fitting experiment with *SGPA* (bold dots). A position marked indicates the translated O10' from the anion. An expected atomic position of the O_γ atom of Ser195 (not considered as a part of the modelling experiment) is indicated merely to show the resulting would-be position executing the same transformation as for the seven fitted atoms. Only relevant H atoms are shown

Instead, the conformational characteristics are explained by the stringent requirement of the ionic interaction between the carboxylate/imidazolium ion pair coupled with the attempt of the former group to maintain as many H-bonds as possible (e.g. four H-bonds, cf. Ref. 75c). Such an attempt is obviously supported by the intramolecular H-bond in *1* · Im · 2 H_2O. The geometry of the corresponding moieties indicates the presence of strongly interacting ionic species (Fig. 42).

5.1.2 Inter-associate (Packing) Relations in *1* · Im · 2 H_2O

Packing in *1* · Im · 2 H_2O also shows some distinct features that may be related to the existence of the ionic species in the crystal. Hydrogen bonding is, of course, a primary feature (Fig. 43). An extensive network exists in this crystal which has the form of endless chains rather than that of loops usually found for the similarly double-faced (H-bond donor and acceptor) alcohols (cf. Fig. 19). As already mentioned, the carboxylate function has four connections, while its neutral —COOH neighbor maintains three H-bond contacts. The inner water molecule with respect

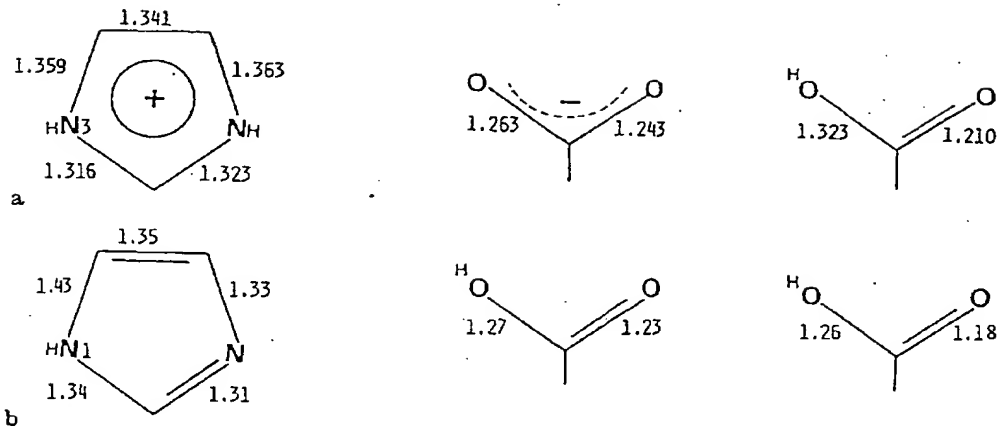


Fig. 42. Relevant dimensions (a) in the dihydrate and (b) in the anhydrous associates of *1* with imidazole [111] [e.s.d's are in the range 0.001–3 and 0.010–14 Å for (a) and (b), respectively]

to the cation is engaged in a full binding capacity (double acceptor and donor), whereas the distant one has only three contacts (double donor, single acceptor). It is relevant to note that all but one of the H-atoms of the cationic C—H groups are involved in well-defined C—H ... O contacts as classified by Taylor and Kennard [75b] (Table 24). This possibly important feature has not been considered hitherto, e.g. in an NMR study for the especially important C(2) atom of the imidazolium moiety [121]. The H-bonds in *1* · Im · 2 H_2O have rather acceptable geometries and indicate strong interactions.

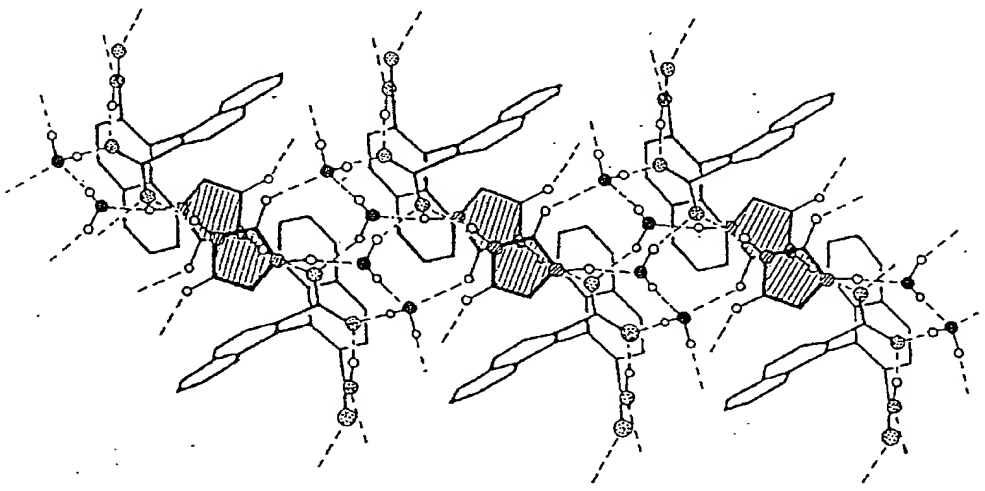


Fig. 43. Packing in the crystal structure of the *1* · imidazole · 2 H_2O associate viewed from the *c* direction [111]. Observe the layer-like arrangement of water molecules near $x = 0$ (H-bonds are indicated as broken lines; only relevant H atoms are shown; O atoms of the host are dotted; water oxygen as a bold circle; N atoms are hatched; the hatched segments signify the imidazole rings)

Table 24. H-bond dimensions in the dihydrated and unhydrated *I* · imidazole associates[a]

Donor-H	D—H (Å)	D—H ... A (deg)	A ... H (Å)	Acceptor
I · imidazole · H_2O (1:1:2) [*II*]				
O11—H11	1.01(3)	172(2)	1.56(3)	$O11'^{b}_{i}$
OW2—H1W2	1.01(3)	175(2)	1.81(3)	$O11'_{ii}$
OW1—H1W1	0.95(2)	157(2)	1.95(2)	$O10'_{iii}$
N3I—H3I	0.98(2)	163(2)	1.80(2)	$O10'_{i}$
OW1—H2W1	0.94(3)	170(2)	1.87(3)	$OW2_{i}$
C2I—H2I	1.05(2)	140(1)	2.35(2)	$OW2_{iv}$
OW2—H2W2	1.04(4)	171(2)	1.98(2)	$O11_{v}$
N1I—H1I	1.04(3)	175(2)	1.67(3)	$OW1_{i}$
C4I—H4I	1.00(2)	150(2)	2.28(2)	$O10_{vi}$
I · imidazole (1:1) [*Im*]				
O11'—H11'	0.99	152	1.66	$O11_{i}$
O11—H11	1.12	171	1.66	$N3I_{ii}$
N1I—H1I	0.97	155	1.79	$O10_{iii}$
C2I—H2I	0.95	116	2.33	$O10'_{iv}$
C5I—H5I	0.94	164	2.35	$O11'_{iii}$

[a] E.s.d.'s are only given where appropriate. [b] Subscripts referring to symmetry operations relating H-bonded pairs of atoms are as follows: i, x, y, z; ii, $1-x$, $1-y$, $1-z$; iii, $x-1$, y, z; iv, $-x$, $1-y$, $1-z$; v, $x-1$, $1+y$, z; vi, x, $1+y$, z for *II*; i, $1-x$, $-y$, $1-z$; ii, $1-x$, $y-1/2$, $1/2-z$; iii, $-x$, $-y-1/2z-1/2$; iv, x, $1/2-y$, $z-1/2$ for *Im*.

Another conspicuous packing feature is the *sheet*-like arrangement of the water molecules in the present crystal structure (Fig. 43). This may be understood as the structural manifestation of the shielding effect of the solvent molecules arranged into a layer-like pattern and effectively depolarizing the negative charges of the counterfacing carboxylate anions. Such a structural role many be invariably found in the crystal structures containing hydrated proton species [122]. Shielding of the charges arising in this crystal structure may also be affected by the counterfacing naphthyl groups protruding over the symmetry-center-related pair of imidazolium cations. The latter units are parallel and at a distance of 3.4 Å to each other. A further interesting point in the packing is the fact that the crystal structure shows the segregation of the enantiomers of *I* into homochiral strands which fit to each other through symmetry centres yielding the centrosymmetrical crystal structure.

5.1.3 Structural and Electrostatic Similarity of *I* · Im · 2 H_2O to Serine Protease Enzymes

As outlined in Sect. 5.1, the inclusion of two molecules of hydrating water enhanced the belief in the extension of the initially assumed similarity of the carboxyl-imidazole pair to the respective functions in serine proteases. The presence of two to four water molecules (or assigned as such) in this family of enzymes [115,117,118,120] and in *I* · Im · 2 H_2O parallels more recent calculations on the hydration enthalpy of bulky organic cations [123]. According to these results, the most important gain in the hydration enthalpy is encountered when the first two water molecules enter the hydration sphere of such cations. Adding more than four solvent molecules will not cause any further essential change in these systems.

Comparison between the steric arrangement in *1* · Im · 2 H_2O and an enzyme was carried out by the means of the least-squares fitting of the atoms of the imidazolium ring and of the two associated oxygen atomic sites at H-bonding distance originating from the carboxylate moiety and of W(1). For the comparison, the bacterial enzyme *Streptomyces Griseus Protease A (SGPA)* was chosen in the native form [124] since this species makes available one of the best resolved structures of the serine protease family. The comparison also relates to a peptide-aldehyde inhibited form of this enzyme [118b]. The respective atomic sites involved the imidazole ring of His57, the Oδ1 atom of Asp102, and a water molecule (W184) of the native enzyme. Results of the least-squares fitting revealed appreciable positional agreement with a mean deviation of less than 0.27 Å for the seven adjusted atomic sites (Fig. 41) [111].

Looking for further similarities, a second water site of *SGPA* (W210) was considered. This W210 is in H-bonding distance from the W184 site. Both positions are considered to mimic the carboxylate-oxygen atomic sites of a would-be transient product of the enzymic cleavage procedure. Upon transformation into the lattice of *1* · Im · 2 H_2O (Fig. 41) the W210 site falls into a place occupied by an O10′ atom within 0.4 Å. This site belongs to one of the carboxylate oxygens of *1* and is related by a unity translation along the crystallographic *a* axis to the other O10′ site which is supposed to be the Oδ1 aspartic carboxylate. Thus, in the crystal structure of *1* · Im · 2 H_2O an atom with a partial negative charge adopts the same steric position as W210 in the native *SGPA*. This fact may draw attention to the interpretation of solvent atomic sites in extremely big structures. This interpretation may be biased, similar to the results with subtilisin [115] and α-chymotrypsin [120] where the presence of even sulphate anions close to the His57 function were found in subsequent studies.

The fitting was not successful for the peptide-aldehyde inhibited form of the *SGPA* enzyme underlining the alignment difference between the active site residues His57 and Asp102 between the two forms of this enzyme (cf. Ref. 118).

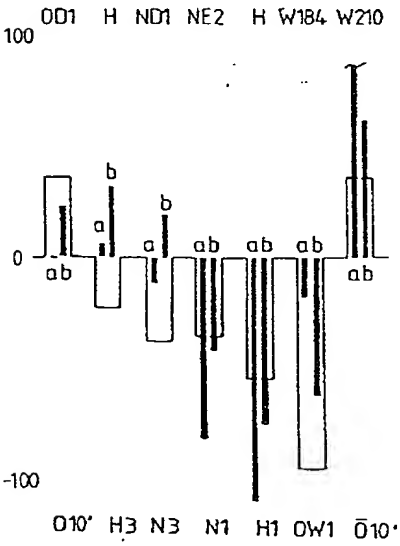


Fig. 44. Electrostatic potential (kJ/mol) pattern in *1* · imidazole · 2 H_2O (empty bars) and *SGPA* (solid lines) taken at the H-bonded atomic sites in both structures. Letters *a* and *b* for *SGPA* denote the potential values deriving from two different orientations of the H atom of the hydroxyl function of Ser195. The value of the potential in the *a* orientation is +192 kJ/mol at the W210 site (cf. Ref. 111)

The remarkable steric agreement of the respective atomic sites discussed above called for the examination of some electronic properties in the two systems being compared. Electrostatic potential patterns were chosen for their simplicity and the relative ease of accessibility [125]. The crystal structure of *1* · Im · 2 H_2O was decomposed into formic acid, water, and imidazole due to practical considerations and the resulting electrostatic potential pattern was compared to that of the native *SGPA*. Potential values at the atomic sites of the main chain of H-bonds connecting two of the catalytically important residues (Asp102 and His57) were considered. The resulting pattern reflects appreciable qualitative and quantitative similarity between the potentials (Fig. 44).

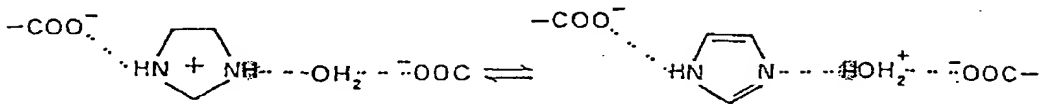
The potential pattern for the enzyme shows high sensitivity with respect to the non-trivial positions of H-atoms at the Oγ-sites of Ser195 of the catalytic machinery. The (— + —) charge distribution characteristic for the tetrahedral intermediate state is reproduced for both models. The decisive feature in this regard is the periodicity of the crystal structure in *1* · Im · 2 H_2O which results in the positive maxima due to the O10′ sites, apart from a unit cell edge. Correspondingly, it is unexpected that the value at the enzyme W210 site is even more positive (Fig. 44). A possible conclusion from the steric and electrostatic similarity is that probably a (— + —) charge distribution already exists in the native *SGPA* enzyme with the second negative charge being carried by an anion at the W210 site similar to sulphate anions in the active site of subtilisin [115].

In conformity with this reflection, trypsin [117b], elastase [126] and subtilisin [115] were found to retain sulphate anions associated with the active site over a pH-range between 5 and 7.5. Curiously, the binding of the anions is stronger on the acidic side of the pH-range. This is an especially interesting observation. It contrasts to the expectations prohibiting the presence of anions at pH values well below 7. The result may indicate that considerations based on common chemical arguments will not necessarily apply to *SGPA* [127]. One is inclined to believe that serine protease enzymes may have the ability to create a micro-environment for their active sites and bind anions more effectively than anticipated.

5.1.4 Water-Mediated Proton Transfer

The discussed analogy between the structures of the simple crystalline model *1* · Im · 2 H_2O and the active site of *SGPA* calls for an examination of the possible role and importance of the water molecules in such structures. The topology of the water molecules in the hydrated associate resembles those found for the hydrated proton structures containing H_3O^+ and $H_5O_2^+$ species [122]. Such cations probably play an essential role in the extremely fast proton transfer observed in liquid water [114,128]. Recent quantum chemical studies throw light on such events in different model systems [128c,129,130]. An H-bonded water molecule in an amidine/water system was shown to work as a mediator at a moderate energy expense [129]. The conditions compare well with the energy balance shown in Scheme 2 [111]. Another supporting observation was made from the study of a 2-pyridone-dihydrate structure [130]. In that case, the existence of a $H_5O_2^+$ ion was in fact corroborated as the proton-

transferring agent, with a tempting steric similarity between the arrangement of the contributing water molecules and *1* · Im · 2 H_2O.



Scheme 2. Hypothetical proton removal path in the *1* · imidazole · 2 H_2O associate [111]

Water molecules or anions close to the active sites in the protease enzymes, mentioned above, may not be considered circumstantial, but may effectively contribute to the removal of the surplus proton from the imidazolium cation before the actual catalytic event. They could serve well to create the initial ion/neutral form of the Asp102-His57 couple which is important for the initial step of the catalytic process in most discussions [116,118,131]. Such a proton removal may be caused by the productive binding of a true substrate (or inhibitor) of the enzyme to the neighboring recognition clefts of the active site.

5.2 Crystal Structure of the Anhydrous 1:1 Associate of *1* with Imidazol · [*1* · Im]

The importance of water in the preceding structure and theoretical considerations of its role suggested growing crystals in a water-free environment. The resulting crystals of unhydrated *1* · Im were, in general, hardly suitable for X-ray analysis. Nevertheless, out of interest, data collection from a rather small crystal was attempted. The subsequent analysis gave the structural model [111] as depicted in Fig. 45.

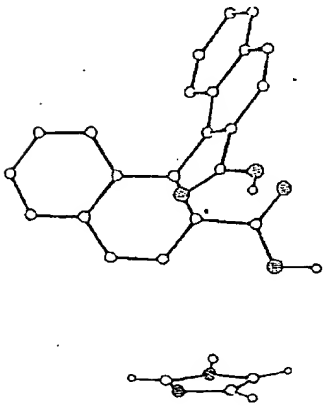


Fig. 45. Molecular structure of the anhydrous imidazole associate of *1* [111] (H atoms of the carboxyl groups indicate putative atomic positions only; O atoms dotted; N atoms hatched)

5.2.1 Intra-associate Relation in *1* · Im (1:1)

It is of importance to discuss briefly the present *1* · Im structure in comparison with the preceding hydrated analogue and with other inclusion ensembles of *1*. Some differences between corresponding dimensions of *1* and imidazole in *1* · Im · 2 H_2O

are shown in Fig. 42. The data given for *1* · Im supports the presence of a neutral rather than a salt-like associate. This important difference can also be noted in the alignment of the —COOH groups with respect to their naphthyl moieties and to each other (see Table 20 in Sect. 4.5.1). The values of the former parameter clearly relate this anhydrous imidazole associate to the common neutral host-guest ensemble of *1*. Dihedral angles in the given range fall under the inclusions of voluminous guest molecules (cf. *1* · 2-BuOH, *1* · t-BuOH, or *1* · DMSO). The mutual orientation of the —COOH groups are also different between the hydrated and the unhydrated forms. The internal H-bridge between the carboxylate and the neutral acid group in *1* · Im · 2 H_2O (cf. Fig. 41) cannot form in the unhydrated *1* · Im due to the unfavorable —COOH alignment (Fig. 45).

5.2.2 Packing and Energy Relations in *1* · Im (1:1): Structural Model for Logic Circuits at the Molecular Level

The H-bonding in the anhydrous *1* · Im (Table 24) has topologic properties (Fig. 46) similar to those in the alcohol coordinatoclathrates of *1* with 1:2 host:guest stoichiometry (cf. Fig. 17a). Assuming a perfectly ordered crystal lattice, the resulting central loop of H-bonds should appear to have homodromic directionality with the donor/acceptor functions separated in space. This contrasts to the behavior in the dihydrated *1* · Im where no such characteristic loops are formed. Involvement of the C—H hydrogen atoms of the imidazole molecule, however, is similar in both cases.

An interesting aspect of the present arrangement arises in connection with the poor quality of the data set and at the same time the reliability of H-atom positions. These are included in the scattering model with a fair amount of ambiguity in their positions, more than usual in X-ray experiments. Certain abnormalities in the geometry of the carboxyl groups may be understood as a result of conformational

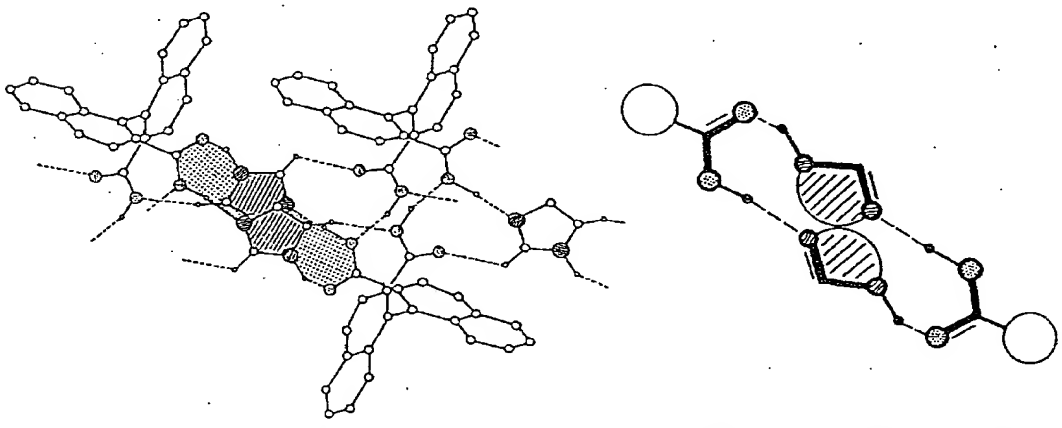


Fig. 46. Characteristics of the packing arrangement in unhydrated *1* · imidazole with a separate schematics emphasizing the central loop topology[111] (H-bonds are indicated as broken lines; backbone H atoms are omitted; O atoms dotted; N atoms hatched; the hatched segments in the schematic drawing signify the imidazole rings)

disorder resulting in the irregular interchange of C—O and C=O moieties at symmetry equivalent positions of the lattice. Averaging of C—O and C=O bonds in the crystal of unhydrated *1* · Im may lead to bond lengths as in Fig. 42. Such dimensions may, of course, arise when at least some of the molecules are in the ionized (salt-type) state. It is virtually impossible to distinguish these effects from each other from X-ray data unless crystals of high quality are provided.

Another peculiarity in the arrangement of the central loop (Fig. 46) is the close resemblance to the arrangement proposed for a theoretically constructed molecule to be used as a molecular flip-flop gate [132]. Such an imaginary molecule would consist of two hemiquinone moieties bound covalently to a central bisimidazolyl nucleus. The central H-bond loop satisfies most of the formal steric and electronic requirements for the proposed proton switching machinery. Indeed, theoretical calculations for this model indicate relatively little energy difference between the ionized and the neutral forms, which may be overcome by the energy of thermal motion [111]. Thus, the apparently small energy differences may also contribute to the assumed coexistence of salt-type and neutral forms which account for the low order in the structure of anhydrous *1* · Im.

6 Conclusions and Prospects

In short, the principle of coordinative assistance in clathrate formation whose possible advantages compared with the classical clathrate type are unfolded in Sect. 2.2 stood the test. It was shown that molecules related to the geometry of scissors and roofs, suitably equipped with functional groups, are nearly perfect host systems providing many clathrates of high stability and with designed selectivity. Hosts derived from other geometric figures and using other functional groups, still connected with the discussed principle, are imaginable in almost any number. In this respect, the coordinatoclathrates described here have added a new dimension to the inclusion chemistry with crystals [7], namely the relationship of polar site (functional group) complementarity between host and guest molecules (cf. Refs. 100 and 101).

On considering future prospects, it is advisable to visualize main aspects to be learned from this study in a more detailed way. The first conclusion is that closely homologous host compounds do form solid heteromolecular associates which, as documented by their crystal structures, are built in a systematic and nearly analogous manner. In other words, this means that in much the same way chemical reactions involving analogously functionalized compounds occur in an analogous (and predictable) manner (homology principle), the crystal chemistry of heteromolecular associates also possesses this feature, extending beyond the boundaries of individual molecules. Moreover, it is seen that there is a definable recognition in heteromolecular assemblies [67a], corresponding to the main structural motifs that one observes. In accord with the term *supramolecular chemistry* coined by Lehn for mostly *ionic* types of host/guest assemblies (cryptates, coronates, speleates, etc.) [100], we are now fairly confident in predicting a further expansion of the boundaries of this new discipline into the more puzzling and promising region of the associates of *neutral* molecules as well [133]. The odds are in our favor that it will soon become possible to predict the outcome of co-crystallization experiments [112].

Another promising point deduced from this study is that structures having a "Gestalt" like those illustrated in this chapter may also be helpful in the design of intramolecularly encapsulating hosts. The simple idea behind this is to translate a fixed multimolecular section of an inclusion lattice into a covalently linked arrangement of building blocks yielding the host. A recent example from another laboratory [134] illustrates the applicability of the crystal model as a useful tool to aid host engineering. The interesting synthetic work performed led to a cross-linked dimer of *26* having virtually the same hydrophobic tunnel geometry as seen in Fig. 32. Many other clathrate structures of this study wait for exploitation in an analogous sense (see also Chapter 4 of this book).

A further subject not fully exploited is the use of crystalline associate formation in artificial enzyme modelling [135]. Certainly, the disclosed structural and electronic relations between the hydrated *1* · imidazole co-crystal and a serine protease enzyme are only the beginning of an imaginable research field. Another proof of this kind has recently been found in the structure of the imidazole associate of *7* [136]. In agreement with the markedly different inclusion behavior of this binaphthyl derivative (see Sect. 4.2.2), *7* will not include water like *1* under the same circumstances. The so formed associate *7* · imidazole (Fig. 47) also deviates in structure and in packing from that of the imidazole associate of *1*. In spite of the lack of water, *7* · imidazole displays a salt-type structure. The resulting crystals are enantiomorphous (space group *P*1) indicating spontaneous resolution on crystallization which is a further difference to *1*. Moreover, the so-formed aggregate will not match when attempts are made to fit it to the respective atomic sites of *SGPA*. It fits, however, with a mean deviation of 0.6–0.7 Å, to some atoms of the subtilisin active site [136]. It was noticed that the similar active sites of the serine proteases are by no means identical [115]. Hence,

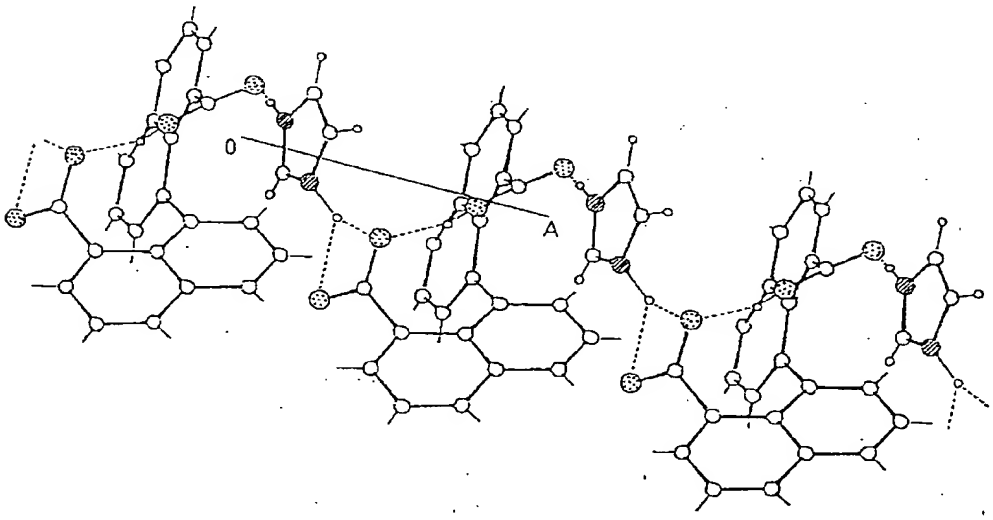


Fig. 47. Molecular structure and packing in the crystalline *7* · imidazole (1:1) associate with an indication of the H-bonding network [136] (H-bonds as broken lines; backbone H atoms of the host are shown as sticks only; O atoms dotted; N atoms hatched)

another challenge arises, namely, to attempt to understand minor alterations occuring in such related systems.

Conglomerate crystallization in the above case indicates that the inclusion approach may be further extended into the realm of the salt-type associates. Such an attempt is especially interesting due to the obvious role in enantiomer separation which relies heavily on the solubility difference of the enantiomeric salts under certain circumstances [137].

It goes without saying, that all the aspects pointed out give rise to a great number of applications in industrial and academic sectors [138]. In future, the use of specific computer programs [139] will help to reach some of the goals more easily.

7 Acknowledgements

The authors are very much indebted to Dr. I. Csöregh (University of Stockholm, Arrhenius Laboratory) for intensive and fruitful cooperation over many years and to Prof. P. Kierkegaard (Stockholm), and Prof. A. Kálmán (Budapest) for their continous interest in and support of this research. The authors would also like to thank Dipl. Chem. M. Hecker and Dipl. Chem. W. Seichter for drawing the figures, and Mrs. M. Weber for the trouble with the typing of the manuscript. The work at Bonn was financially supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

8 References

1. Hall, D. M., Turner, E. E.: J. Chem. Soc. *1955*, 1242
2. Weber, E., Csöregh, I., Stensland, B., Czugler, M.: J. Am. Chem. Soc. *106*, 3297 (1984)
3. An experimental note of Ref. 1 only vaguely suggests possible "solvate formation"
4. Encyclopaedia Britannica USA, Instant Service Report R-1519, Britannica Centre, 310 South Michigan Ave, Chicago, IL 60604
5. Brown Jr., J. F.: Sci. Am. *207*, 82 (1962)
6. Saenger, W.: Umschau *74*, 635 (1974)
7. Atwood, J. L., Davies, J. E. D., MacNicol, D. D. (eds.): Inclusion Compounds, Vols. 1–3, London, Academic Press 1984 [8]
8. Recent and most comprehensive representation of this topic. A complete reference list of monographies and reviews on clathrate compounds is found in Chapter 1 of Vol. 140 of this series (Molecular Inclusion and Molecular Recognition — Clathrates I)
9. Schlenk Jr., W.: Fortschr. Chem. Forsch. *2*, 92 (1951)
10. Cramer, F.: Angew. Chem. *64*, 437 (1952)
11. Takemoto, K., Sonoda, N. in: Vol. 2 of Ref. 7, p. 47
12. Smith, A. E.: Acta Crystallogr. *5*, 224 (1952)
13. Giglio, E. in: Vol. 2 of Ref. 7, p. 207
14. Popovitz-Biro, R., Chang, H. C., Tang C. P., Shochet, N. R., Lahav, M., Leiserowitz, L.: Pure Appl. Chem. *52*, 2693 (1980)
15. Powell, H. M. in: Non-stoichiometric Compounds, Mandelcorn, L. (ed.), New York—London, Academic Press 1964, p. 438
16. MacNicol, D. D. in: Vol. 2 of Ref. 7, p. 1
17. Bhatnagar, V. M.: Clathrate Compounds, New Delhi, S. Chand 1968, p. 16
18. Jeffrey, G. A. in: Vol. 1 of Ref. 7, p. 135
19. Weber, E., Josel, H.-P.: J. Incl. Phenom. *1*, 79 (1983)

20. Hyatt, J. A., Duesler, E. N., Curtin, D. Y., Paul, I. C.: J. Org. Chem. *45*, 5074 (1980); Rahman, A., van der Helm, D.: Cryst. Struct. Commun. *10*, 731 (1981); Thierbach, D., Huber, F.: Z. Anorg. Allg. Chem. *477*, 101 (1981); Mac, T. C. W.: J. Chem. Soc., Perkin Trans. 2, *1982*, 1435; Mentzafos, D., Terzis, A., Filippakis, S. E.: Cryst. Struct. Commun. *11*, 71 (1982); Pickering, M., Small, R. W. H.: Acta Crystallogr. B *38*, 3161 (1982); Shiel, H. S., Hoard, L. G., Nordmann, C. E.: Acta Crystallogr. B *38*, 2411 (1982)
21. "Fourth International Symposium on Inclusion Phenomena and Third International Symposium on Cyclodextrins", July 20–25, 1986, Lancaster (cf. Coll. Abstr.)
22. Davies, J. E. D., Kemula, W., Powell, H. M., Smith, N. O.: J. Incl. Phenom. *1*, 3 (1983)
23. Fischer, E.: Ber. Dtsch. Chem. Ges. *27*, 2985 (1894)
24. Cram, D. J. in: Applications of Biochemical Systems in Organic Chemistry, Part II, Techniques of Chemistry, Vol. X, Jones, J. B., Sih, C. J., Perlman, D. (eds.), New York, Wiley Interscience 1976, p. 815
25. E.g. Allcock, H. R., Allen, R. W., Bissell, E. C., Smeltz, L. A., Teeter, M.: J. Am. Chem. Soc. *98*, 5120 (1976); Löhr, H.-G., Vögtle, F., Schuh, W., Puff, H.: J. Chem. Soc., Chem. Commun. *1983*, 924; Herbstein, F. H., Mak, T. C. W., Reisner, G. M., Wong, H. N. C.: J. Incl. Phenom. *1*, 301 (1984)
26. Kitaigorodsky, A. I.: Order and Disorder in the World of Atoms, The Heidelberg Science Library, Vol. 3, New York, Springer Verlag 1967
27. Kitaigorodsky, A. I.: Molecular Crystals and Molecules, New York—London, Academic Press 1973
28. Kitaigorodsky, A. I.: Mixed Crystals, Berlin—Heidelberg—New York—Tokyo, Springer Verlag 1984
29. With reference to graphic arts, see: Die Welten des M. C. Escher, Hersching, Manfred Pawlak Verlagsgesellschaft 1971, 3rd ed.
30. Recent examples of host molecules with C_2-symmetry from other laboratories: Chan, T. L., Mak, T. C. W., Trotter, J.: J. Chem. Soc., Perkin Trans. 2, *1980*, 672; Mann, B. J., Paul, I. C., Curtin, D. Y.: J. Chem. Soc., Perkin Trans. 2, *1981*, 1583; Zheng Huang, N., Mak, T. C. W.: J. Chem. Soc., Chem. Commun. *1982*, 543; Bishop, R., Dance, I. G., Hawkins, S. C.: J. Chem. Soc., Chem. Commun. *1983*, 889; Radcliffe, M. D., Gutiérrez, A., Blount, J. F., Mislow, K.: J. Am. Chem. Soc. *106*, 682 (1984)
31. Baker, W., Gilbert, B., Ollis, W. D.: J. Chem. Soc. *1952*, 1443
32. Grasselli, J. G. (ed.): Atlas of Spectral Data and Physical Constants for Organic Compounds, Cleveland, Ohio, The Chemical Rubber Co. 1973; see also Davies, J. E. D. in: Vol. 3 of Ref. 7, p. 37
33. Guest selectivity properties to this extent are out of the ordinary, cf. Ref. 7
34. Reichardt, C.: Solvent Effects in Organic Chemistry, Weinheim, Verlag Chemie 1979
35. Hall, D. M., Ridgewell, S., Turner, E. E.: J. Chem. Soc. *1954*, 2498
36. Optically resolved compound, see: Mislow, K., Glass, M. A. W., O'Brien, R. E., Rutkin, P., Steinberg, D. H., Weiss, J., Djerassi, C.: J. Am. Chem. Soc. *84*, 1455 (1962)
37. Weber, E., Ahrendt, J., Finge, S.: unpublished result (1986)
38. Pummerer, R., Prell, E., Riede, A.: Ber. Dtsch. Chem. Ges. *59*, 2159 (1926)
39. Weil, K., Kuhn, W.: Helv. Chim. Acta *27*, 1648 (1944); Barber, H. J., Gaimster, K.: J. Appl. Chem. *2*, 565 (1952)
40. Cf. Akimoto, H., Yamada, S.: Tetrahedron *27*, 5999 (1971)
41. Brass, K., Sommer, P.: Ber. Dtsch. Chem. Ges. *61*, 997 (1928)
42. Koukotas, C., Schwartz; L. H.: J. Chem. Soc., Chem. Commun. *1969*, 1400; see also Bell, F., Waring, D. H.: J. Chem. Soc. *1949*, 2689
43. Haas, G., Prelog, V.: Helv. Chim. Acta *52*, 1202 (1969)
44. Toda, F., Tanaka, K., Nagamatsu, S.: Tetrahedron Lett. *25*, 4929 (1984); Toda, F., Tanaka, K., Mak, C. W.: Chem. Lett. *1984*, 2085
45. Bromobenzene solvate of optically resolved dimethylester of *16*, see: Akimoto, H., Iitaka, Y.: Acta Crystallogr. B *25*, 1491 (1969)
46. Schwenk, A.: Chem.-Ztg. *53*, 335 (1929)
47. With current knowledge, possible clathrate formation of *22* with ethanol may be anticipated from the original synthetic description in Ref. 43
48. Czugler, M., Stezowski, J. J., Weber, E.: J. Chem. Soc., Chem. Commun. *1983*, 154

49. Neupert-Laves, K., Dobler, M.: Helv. Chim. Acta *64*, 1653 (1981)
50. Czugler, M., Weber, E., Ahrendt, J.: J. Chem. Soc., Chem. Commun. *1984*, 1632
51. Mowry, D. T.: J. Am. Chem. Soc. *69*, 573 (1947); Hurd, D. C., Tockman, A.: J. Am. Chem. Soc. *81*, 116 (1959); Baumgartner, P., Hugel, G.: Bull. Soc. Chim. Fr. *1954*, 1005; Walborskiy, H. M.: Helv. Chim. Acta *36*, 1251 (1953)
52. Barnett, E. D. B., Goodway, N. F., Lawrence, C. A.: J. Chem. Soc. *1935*, 1102; Scheibler, H., Scheibler, U.: Chem. Ber. *87*, 379 (1954); see also Ref. 51
53. Bachmann, W. E., Scott, L. B.: J. Am. Chem. Soc. *70*, 1458 (1948)
54. Bachmann, W. E., Cole, W.: J. Org. Chem. *4*, 60 (1939); Johnson, W. K., Patton, T. L.: U.S. 2,938,049, May 24, 1960 [Chem. Abstr. *54*, 19628i (1960)]
55. Figeys, H. P., Dralants, A.: Tetrahedron Lett. *28*, 3031 (1972); Huebner, C. F.: Ger. Off. 1,914,998, Oct. 30, 1969 [Chem. Abstr. *72*, 78769p (1970)]
56. Sakellarios, E., Kyrimis, T.: Ber. Dtsch. Chem. Ges. *57*, 322 (1924); Wilson, K. R., Pincock, R. E.: J. Am. Chem. Soc. *97*, 1474 (1975)
57. Maigrot, N., Mazaleyrat, J. P.: Synthesis *1985*, 317; Tamao, K., Minato, A., Miyake, N., Matsuda, T., Kiso, Y., Kumada, M.: Chem. Lett. *1975*, 133
58. Bergmann, F., Eschinazi, H. E., Neeman, M.: J. Org. Chem. *8*, 179 (1943)
59. Ueji, S., Nakatsu, K., Yoshioka, H., Kinoshita, K.: Tetrahedron Lett. *23*, 1173 (1982)
60. Badar, Y., Cheung King Ling, C., Cooke, A. S., Harris, M. M.: J. Chem. Soc. *1965*, 1543
61. Kress, R. B., Duesler, E. N., Etter, M. C., Paul, I. C., Curtin, D. Y.: J. Am. Chem. Soc. *102*, 7709 (1980)
62. Newman, M. S.: J. Am. Chem. Soc. *62*, 1683 (1940)
63. Bell, F., Waring, D. H.: J. Chem. Soc. *1949*, 267, 1579
64. Weber, E., Ahrendt, J., Czugler, M., Csöregh, I.: Angew. Chem. *98*, 719 (1986); Angew. Chem., Int. Ed. Engl. *25*, 746 (1986)
65. Dale, J.: Stereochemie und Konformationsanalyse, Weinheim, Verlag Chemie 1978
66. Clarkson, R. G., Gomberg, M.: J. Am. Chem. Soc. *52*, 2881 (1930)
67. (a) Czugler, M.: Transactions of the "Symposium on Molecular Structure: Chemical Reactivity and Biological Activity", Beijing, China 1986, Oxford, University Press, to be published (1988)
    (b) For example, a ternary aggregate was reported for a *32*-related host compound [code ANTTCN in the Cambridge Crystallographic Database: 9,10-dihydro-9,10-ethanoanthracene-11,11,12,12-tetracarbonitrile-tetracyanoethylene complex methylene chloride solvate, $8(C_{20}H_{10}N_4):(C_6N_4):2(CH_2Cl_2)$]. See Karle, I. L., Fratini, A. V.: Acta Crystallogr. B *26*, 596 (1970)
68. Crystal structure of 1,1′-binaphthyl-8,8′-dicarboxylic acid: Czugler, M., Weber, E.: Unpublished result (1985)
69. Crystal structure of bis-β-naphthol: Gridunova, G. V., Furmanova, N. G., Shklover, V. E., Struchkov, Yu. T., Ezhkov, Z. I., Chayanov, B. A.: Kristallografiya *27*, 477 (1982)
70. Crystal structure of 2,2′-bis(hydroxymethyl)-1,1′-binaphthyl: Czugler, M., Csöregh, I., Weber, E.: Unpublished result (1984)
71. Csöregh, I., Czugler, M., Weber, E.: Transactions of the "Symposium on Molecular Structure: Chemical Reactivity and Biological Activity", Beijing, China 1986, Oxford, University Press, to be published (1988)
72. Racemic 1,1′-binaphthyl: Kerr, K. A., Robertson, J. M.: J. Chem. Soc. B *1969*, 1146
73. Optically active 1,1′-binaphthyl: Kuroda, R., Mason, S. F.: J. Chem. Soc., Perkin Trans. 2, *1981*, 167. See also Ref. 61
74. Crystal structure of 9,9′-spirobifluorene: Csöregh, I., Czugler, M., Weber, E.: Unpublished result (1985)
75. Recent literature on H-bonds:
    (a) Taylor, R., Kennard, O.: Acc. Chem. Res. *17*, 320 (1984)
    (b) Taylor, R., Kennard, O.: J. Am. Chem. Soc. *104*, 5063 (1982) (C—H ... X type H-bonds)
    (c) Taylor, R., Kennard, O., Versichel, W.: ibid. *105*, 5761 (1983)
    (d) Taylor, R., Kennard, O., Versichel, W.: ibid. *106*, 244 (1984)
    (e) Taylor, R., Kennard, O., Versichel, W.: Acta Crystallogr. B *40*, 280 (1984)

(f) Murray-Rust, P., Glusker, J. P.: J. Am. Chem. Soc. *106*, 1018 (1984)
(g) Berkovitch-Yellin, Z., Ariel, S., Leiserowitz, L.: J. Am. Chem. Soc. *105*, 765 (1983)
76. Saenger, W.: Nature (London) *279*, 343 (1979); Lindner, K., Saenger, W.: Acta Crystallogr. B *38*, 203 (1982) and references therein
77. Crystal structure of *1* with 1-propanol (2:1): Czugler, M., Weber, E.: Unpublished result (1983)
78. Clementi, E.: "Structure of water and counterions for nucleic acids in solution", in: Structure and Dynamics: Nucleic Acids and Proteins, Clementi, E., Sarma, R. H. (eds.), New York, Adeline Press 1983
79. Crystal structure of the acetic acid inclusion of *1*: Csöregh, I., Weber, E.: Unpublished result (1985)
80. Crystal structures of the *7* · pyridine (1:1), *7* · 2-(hydroxymethyl)-pyridine (1:1), and *7* · pyridine · acetic acid (1:1:1) aggregates: Csöregh, I., Czugler, M., Weber, E.: Unpublished results (1984)
81. Crystal structure of *13* · imidazole: Czugler, M., Weber, E.: Unpublished result (1985)
82. Csöregh, I., Sjögren, A., Czugler, M., Cserzö, M., Weber, E.: J. Chem. Soc., Perkin Trans. 2, *1986* 507
83. Crystal structure of *25b* · DMF (1:1): Czugler, M., Weber, E.: Unpublished result (1983)
84. (a) Bernstein, F. H., Marsh, R. E.: Acta Crystallogr. B *33*, 2358 (1977)
(b) Bernstein, F. H., Kapon, M.: ibid. *34*, 1608 (1978)
(c) Bernstein, F. H., Kapon, M., Wasserman, S. ibid. *34*, 1613 (1978)
(d) Bernstein, F. H., Kapon, M.: ibid. *35*, 1614 (1979)
85. Crystal structure of *20* · DMSO: Csöregh, I., Czugler, M., Weber, E.: Unpublished result (1985)
86. Csöregh, I.: Personal communication (1987)
87. Crystal structure of *41* · DMSO (1:2): Czugler, M., Csöregh, I., Weber, E., Ahrendt, J.: Unpublished result (1986)
88. Gold, V., Stahl, R., Wassef, W. N., Kuroda, R.: J. Chem. Soc., Perkin Trans. 2, *1986*, 477
89. Neupert-Laves, K., Dobler, M.: Helv. Chim. Acta *64*, 1653 (1981)
90. Crystal structures of *48* with benzene (1:1) and p-xylene (2:1): Czugler, M., Weber, E., Csöregh, I.: Unpublished results (1986)
91. Gavezzotti, A.: Personal communication (1985). See also Gavezzotti, A., Simonetta, M. in: Organic Solid State Chemistry (Studies in Organic Chemistry, Vol. 32), Desiraju, G. R. (ed.), Amsterdam—New York, Elsevier 1987, p. 391
92. Gridunova, G. V., Furmanova, N. G., Shklover, V. E., Struchkov, Yu. T., Ezhkova, B. A., Chayanov, B. A.: Kristallografiya, *27*, 477 (1982)
93. Harata, K., Tanaka, J.: Bull. Chem. Soc. Jpn. *46*, 2747 (1973)
94. Pauptit, R. A., Trotter, J.: Can. J. Chem. *61*, 69 (1983)
95. Gridunova, G. V., Shklover, V. E., Struchkov, Yu. T., Chayanov, B. A.: Kristallografiya *28*, 87 (1983)
96. Wells, J. L., Trus, B. L., Johnston, R. M., Marsh, R. E., Fritchie, C. J., Jr.: Acta Crystallogr. B *30*, 1127 (1974)
97. Pauptit, R. A., Trotter, J.: Can. J. Chem. *59*, 1149 (1981)
98. Pauptit, R. A., Trotter, J.: ibid. *59*, 1149 (1981)
99. Fink, R., van der Helm, D.: Cryst. Struct. Commun. *9*, 97 (1980)
100. Lehn, J.-M.: Science, *227*, 849 (1985); Lehn, J.-M.: Angew. Chem. *100*, 91 (1988); Angew. Chem., Int. Ed. Engl. *27*, 89 (1988)
101. Cram, D. J.: Angew. Chem. *98*, 1041 (1986); Angew. Chem., Int. Ed. Engl. *25*, 1039 (1986)
102. Lipscomb, W. N.: Acc. Chem. Res. *15*, 232 (1982)
103. See Chapters 2 and 3 in Vol. 140 of this series (Molecular Inclusion and Molecular Recognition — Clathrates I)
104. For a comprehensive review of the packing modes of aliphatic carboxylic acids, see: Leiserowitz, L.: Acta Crystallogr. B *32*, 775 (1976)
105. On the symmetry of self-complementary surfaces, see e.g.: Morgan, R. S., Miller, S. L., McAdon, J. M.: J. Mol. Biol. *127*, 31 (1979)
106. Gavezzotti, A.: J. Am. Chem. Soc. *105*, 5220 (1983)
107. Sturtevant, J. M.: Proc. Natl. Acad. Sci. U.S.A. *74*, 2236 (1977)
108. Recent examples of artificial enzyme models based on the β-cyclodextrin skeleton: